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PerkinElmer Solidifies OUS Presence With $1.3bn EUROIMMUN Buy

TINA TAN tina.tan@informa.com


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PerkinElmer Inc. has agreed to acquire **EUROIMMUN Medical Laboratory Diagnostics AG**, a German multinational specializing in autoimmune, infectious disease and allergy testing.

One key benefit for PerkinElmer from the $1.3bn all-cash deal is the Waltham, Mass., firm will significantly grow its geographic reach outside the US. Of the about $310m in revenue Lubeck, Germany-based EUROIMMUN generated in 2016, 45% came from China, 30% from its Europe, Middle East & Africa business and 20% from "rest-of-world" markets, including India. Only 5% of EUROIMMUN's revenue came from the US, while PerkinElmer has an extensive presence in the US through its market-leading position in reproductive health. The firm says it will be leveraging these US channels to introduce and sell EUROIMMUN's products.

In the deal, PerkinElmer will gain a robust business – EUROIMMUN has an average top-line, all-organic growth of 19% over the last five years and EBITDA margins that are said to be "slightly higher than PerkinElmer's, PerkinElmer officials said during an investor conference call. EUROIMMUN is expected to generate around $350m in revenue in 2017.

"In addition to these and other commercial synergies, EUROIMMUN increases our addressable market and enables the combined company to offer more complete solutions," PerkinElmer President and CEO Robert Friel told investors. "For example, EUROIMMUN enables expansion in the nearby adjacencies within reproductive health, including sexually transmitted diseases, HPV and infectious disease, while increasing PerkinElmer's ability to offer an extensive menu and more complete solutions to our customers."

EUROIMMUN brings a sizeable portfolio to PerkinElmer. Within autoimmune testing, the firm has more than 70 assays and 100 tests for identifying medical conditions across the broad range of practices, including dermatology, gastroenterology and rheumatology. In infectious diseases, EUROIMMUN's focus is on emerging diseases, including Zika, dengue, chikungunya, MERS and pregnancy-related infections. "Over 90% of [EUROIMMUN's] sales come from recurring reagents, as one of its strength is the ability to rapidly develop assays and introduce new diagnostic tests in response to newly identified health conditions, and critical customer needs," said Friel. In allergy testing, the company has a menu for evaluating more 650 allergens for environmental and food allergies.

PerkinElmer will have to compete with some notable heavyweights in the autoimmune and allergy testing markets, including Abbott Labs, Siemens Healthineers, Thermo Fisher (through Phadia, which it acquired in 2011), Bio-Rad Laboratories and Inova Diagnostics (owned by Werfen Group).

The transaction will also bring tax benefits to PerkinElmer, allowing the company to use both current and future overseas cash more efficiently, added Friel. The firm will fund the transaction with existing cash, plus around $900m of incremental debt via its existing revolver.

For all of 2016, PerkinElmer's Diagnostics division generated revenue of $603.2m, accounting for approximately 28% of its total revenue (Discovery & Analytical Solutions accounted for the remainder, at $1.51bn). With the addition of EUROIMMUN, the diagnostics

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FROM THE EDITORS OF: **THE GRAY SHEET, CLINICA, START-UP** AND **MEDTECH INSIGHT NEWSLETTER**

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DAVID FILMORE @MEDTECHDAVID
david.filmore@informa.com
TINA TAN @MEDTECHTINATAN
tina.tan@informa.com
SHAWN M. SCHMITT @MEDTECHSHAWN
shawn.schmitt@informa.com
REED MILLER @MEDTECHREED
reed.miller@informa.com
AMANDA MAXWELL @MEDTECHAMANDA
amanda.maxwell@informa.com
MARION WEBB @MEDTECHMARION
marion.webb@informa.com
SUE DARCEY @MEDTECH_INSIGHT
sue.darcey@informa.com
FERDOUS AL-FARUQUE @MEDTECH_DANNY
danny.al-faruque@informausa.com
ELIZABETH ORR @ELIZABETHJORR
elizabeth.orr@informa.com
CATHERINE LONGWORTH @MEDTECHCATE
catherine.longworth@informa.com
ASHLEY YEO @ASHLEYPYEO
ashley.yeo@informa.com
MAUREEN KENNY @SCRIPREGMAUREEN
maureen.kenny@informa.com
NEENA BRIZMOHUN @SCRIPREGNEENA
neena.brizmohun@informa.com
VIBHA SHARMA @SCRIPREGVIBHA
vibha.sharma@informa.com
JANET HANIAK SENIOR DESIGNER
GAYLE REMBOLD FURBERT DESIGN SUPERVISOR
RICHARD FAINT HEAD OF MEDTECH
richard.faint@informa.com
PHIL JARVIS MANAGING DIRECTOR

Editorial office:
52 Vanderbilt Avenue, 11th Floor, New York, NY 10017
phone 240-221-4500, fax 240-221-2561
CUSTOMER CARE:
1-888-670-8900 OR 1-908-547-2200
FAX 646-666-9878
clientservices@pharmamedtechbi.com

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How Israel's Digital Innovators Are Capturing The Minds Of Medtronic And Others

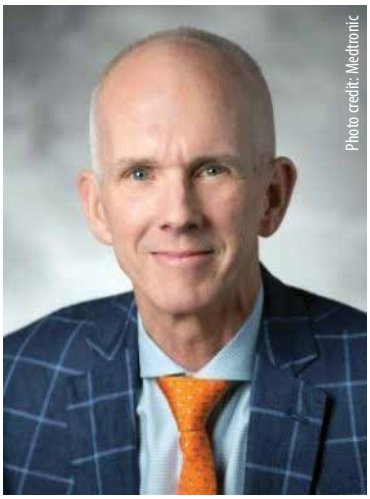
CATHERINE LONGWORTH catherine.longworth@informa.com

With the explosion of Israeli digital health innovation in recent years, it was merely a matter of time before big players began to sit up and take notice. MindUP, a joint venture between **Medtronic PLC**, **IBM**, Pitango Venture Capital, Impact 1st Investments and Rambam Medical Center started activities in March 2016. As Israel's first incubator dedicated to digital health innovation, the program is focused on investment in the areas of big data, predictive analytics, telemedicine, cloud computing, wearable and implantable sensors, advanced point of care diagnostics and personalized medicine.

Through the two-year incubator program, entrepreneurs are promised "360-degree support" to help develop fully fledged companies that can reach market. It's the ideal platform to nurture innovative new technologies, says Paul Hermes, entrepreneur-in-residence at Medtronic's Surgical Innovations unit and a board member of MindUP. Hermes joined Medtronic through its $50bn blockbuster acquisition of Covidien; for the last four years, he has been leading the team that is developing Medtronic's first surgical robot, a project which was first launched at a pre-acquisition Covidien, in a bid to increase the company's access to the minimally invasive surgery market.

Interest in the robotics surgical space has ramped up significantly in the last few years as companies hope to capture a share of the market, which is projected to reach more than $10bn by 2021. **Intuitive Surgical Inc.** remains the longtime market leader and in 2015 alone, reported $2.38bn in revenues and 652,000 procedures performed with its *da Vinci Surgical System*. The company's systems are primarily used in gynecologic, general, urologic, cardiothoracic, and head and neck surgery. *(Also see "Robotic-Assisted Surgery: Taking MIS By Storm" - , 26 May, 2016.)* This field has attracted other medtech heavyweights like **Johnson & Johnson**, which partnered with **Verily Life Sciences** (**Google Inc.**'s former life sciences subsidiary) in March 2015 to form a robotic-assisted surgical platform which was publicly launched as **Verb Surgical Inc.** Meanwhile, the pace of technological advances in this field has quickened with smaller players developing novel technologies that allow robotics to be used for surgery on different, previously-hard-to-operate parts of the anatomy. *(Also see "Ever Decreasing Dimensions, Snakes And Origami: The Next-Gen Surgical Robots" - Medtech Insight, 28 Feb, 2017.)*

"Robotics is a large and rapidly growing field and surgical robotics is a huge opportunity because today there's only really one company that's doing it," says Hermes. "At Medtronic we are focused on technologies that can help more surgeons do minimally invasive surgery. These are the types of technologies that Medtronic want to invest in because that's one of our biggest areas of focus and the legacy from the Covidien business is moving surgery from open, invasive surgery to less invasive procedures – which can include robot- assisted tools."



Paul Hermes, entrepreneur-in-residence Surgical Innovations, Medtronic

As a member of MindUP's board of directors, Hermes is searching for "big ideas" that can have the biggest impact in healthcare. "Medtronic's engagement with MindUP and this community in Israel is about finding answers to problems. Medtronic is trying to move beyond gadgets to more holistic solutions that can advance care and improve value based healthcare. The MindUP venture made sense for Medtronic as we'd had good experiences of business in Israel and were interested in the idea of casting our net a bit wider and the leverage that could be brought from partners like Pitango and the Israel Innovation Authority." Hermes adds that a recent Israeli visit by Medtronic's CEO Omar Ishrak is "testament to our confidence in the technologies" in the country.

MindUP founding-partner, Pitango, is one of Israel's biggest venture capital firm which has invested in some of the country's most successful home-grown medical device companies such as **EarlySense Ltd.**, **LifeBond Ltd.** and **CarboFix Orthopedics**. "What we're seeing is more medical device and digital health companies reaching a significant scale in Israel that we did not see 10 years ago," says Ittai Harel, managing general partner at Pitango. "We have companies reaching tens of millions of dollars of sales and companies that are

Photo credit: Mr. Yoram Reshef

Ittai Harel, managing general partner at Israel's biggest venture capital firm Pitango

completing [US FDA pre-market approvals] and have plans to go beyond that and commercialize which we did not see before."

"Companies are building themselves in a way that they can actually become independent and entertain both M&A or IPO options, reach profitability. If you look back, there were maybe three or four medical device companies in Israel's history that did something like that. Today, just in our portfolio, there's more than that and in Israel in general there're several and more growing companies every day."

However, Israeli start-ups face significant challenges in acquiring capital at home as investors favor later-stage companies over early stage start-ups. "You look at the number of start-ups being formed in medtech and digital health in Israel compared to the US and you look at the capital available for them and its clear Israel is greatly undercapitalized. Many companies are facing greater competition for fewer dollars," says Harel.

Consolidation of the big medtech companies has also created problems for VCs, with fewer buyers for start-ups, says Harel. He adds that this has led to an evolution in the entrepreneurs and the type of companies they set up as the focus is increasingly on "where people think there is more activity or funding or buyers." Harel also notes that there are more non-traditional players active in digital health: "We've seen in the recent five years a number of tech companies such as Google, Apple and Samsung that weren't involved in digital/mobile health before, now moving into the space,"

However, Harel says when companies are finding funding, it's not necessarily coming with "high quality guidance" needed to ensure commercial success. While Israel is famed for its technological innovations, companies are still struggling to differentiate themselves in sales and marketing. "There aren't many Israeli success companies based on prowess of sales and marketing," explains Harel. "The US is known to be better at that, Israel alone is a small market so companies don't get to develop expertise in growing big businesses here."

"The whole idea of MindUP is that you put together the top medical device company in the world [Medtronic], the top analytics healthcare company [IBM], one of the top hospitals in Israel [Rambam] and a venture fund [Pitango] and together we can provide in the first two years a lot more value to start-ups who would usually find themselves alone with private money."

With the backing of big players like Medtronic, IBM, Pitango and Rambam, entrepreneurs are at a major advantage, says Harel. "Many early- stage companies start developing their products with local hospitals and local physicians but it could be a completely different model in the US and Europe and the fact that they surround themselves with folks that are intertwined with global systems gives them a competitive edge," he says.

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Dan Shwarzman, CEO of MindUP

Dan Shwarzman, MindUP CEO adds, "One of the challenges especially with digital health start-ups when they are starting out by themselves is they need to deal with large organisations, companies, hospitals and to do it all without any support, guidance or help. From day one in the incubator they have access to a wealth of knowledge and experience that can guide them and help them navigate their way through the developmental phase until they get to the market."

Harel adds, "This incubator is a unique situation as it provides leading expertise from across the industry. That's the reason why we are seeing really high- quality entrepreneurs including repeat [second-, /third- time] entrepreneurs apply which is very rare to see in other incubators. That's a sign to me that we are doing something right."

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US FDA's New Game Plan For Digital Health

FERDOUS AL-FARUQUE danny.al-faruque@informa.com

US FDA Commissioner Scott Gottlieb announced a coordinated strategy to remove regulatory ambiguity from the burgeoning field of digital health and keep agency device reviewers' hands off new software and mobile apps in as many cases as possible.

Gottlieb outlined his broad-strokes vision in a June 15 blog post, highlighting a plan to implement the software provisions in the 21st Century Cures Act and go beyond them to deregulate where possible, and map out a pilot oversight program that would rely on third-party pre-certification of developers' design and validation procedures.

"In this rapidly changing environment, ambiguity regarding how FDA will approach a new technology can lead innovators to invest their time and resources in other ventures," Gottlieb stated. "To encourage innovation, FDA should carry out its mission to protect and promote the public health through policies that are clear enough for developers to apply them on their own, without having to seek out, on a case-by-case basis, FDA's position on every individual technological change or iterative software development."

Gottlieb had championed a lighter regulatory touch for digital health devices before taking on the commissioner post, as part of a health IT advisory body for the Department of Health and Human Services and as a public commentator. *(Also see "Consumer-'Empowering' Devices Called Out In Gottlieb's First FDA Speech" - Medtech Insight, 16 May, 2017.)*

At least one industry representative said the announcement from Gottlieb was a highly positive development for health software developers. "Holy smokes. It's amazing what an election will do," said Bradley Thompson, counsel for the Clinical Decision Support (CDS) Coalition, an industry group of health-care software developers. "All in all, I feel like I've died and gone to heaven."

FDA's device center has already in recent years advanced policies that favor avoiding active FDA oversight of digital-health tools that are lower risk, but software developers have complained that the policies left too many unanswered questions for future oversight of the space. The Cures Act, enacted in December, aimed to address that by defining specific categories of products, including wellness and clinical administrative support software, that will outside of FDA's jurisdiction. *(Also see "'Cures' Bill Circumvents FDA On Medical Software Regs" - Medtech Insight, 30 Nov, 2016.)*

Gottlieb said June 15 that FDA plans to publish guidance in the coming months to further clarify what falls outside the FDA's regulatory scope and explain how Cures software provisions impact the agency's pre-existing policies.

"FDA will provide guidance to clarify our position on products that contain multiple software functions, where some fall outside the scope of FDA regulation, but others do not," said Gottlieb. "In addition, FDA will provide new guidance on other technologies that, although not addressed in the 21st Century Cures Act, present low enough risks that FDA does not intend to subject them to certain pre-market regulatory requirements.

"Greater certainty regarding what types of digital health technology is subject to regulation and regarding FDA's compliance policies will not only help foster innovation, but also will help the agency to devote more resources to higher risk priorities," he added.

'PRE-CERTIFICATION' PARADIGM

Gottlieb also appeared to put his support behind a new paradigm for regulating digital health tools that agency officials have been floating in recent months. It would be based on certifying a company's internal procedures as a means to providing a quicker, and less costly, route to market.

"While the pilot program is still being developed, we are considering whether and how, under current authorities, we can create a third-party certification program under which lower risk digital health products could be marketed without FDA premarket review and higher risk products could be marketed with a streamlined FDA premarket review," the commissioner explained.

"Certification could be used to assess, for example, whether a company consistently and reliably engages in high quality software design and testing (validation) and ongoing maintenance of its software products," he said.

This aligns closely an "FDA pre-check" program that has been discussed by Bakul Patel, who heads digital health policy within the device center. *(Also see "Software Fast Track? US FDA Asks Developers To Envision 'Precheck' Program" - Medtech Insight, 9 Mar, 2017.)*

Thompson, with the CDS Coalition and also an attorney with Epstein Becker & Green, strongly supports the concept, and says it is one his group has advocated for.

"In advocating for the pre-check idea, we have advanced the notion that software creates certain unique opportunities to

collect data on an almost real-time basis from the marketplace, and make continuous improvement through changes to the software," he said. "We've argued that that strength of the software development model could be used as a basis for creating the expedited pathway to market. It would seem as though FDA is interested in pursuing that line of thought."

In his blog, Gottlieb also goes on to state digital health products could benefit from the National Evaluation System for health Technology (NEST) program that FDA is helping develop in collaboration with partners such as the Medical Device Innovation Consortium (MDIC). If the project gets off the ground and is successful, it is intended to create a new paradigm for medical devices in general where products can be brought to market with less premarket data requirements as long as sponsors provide more supporting post-market real-world evidence for their products.

"Applying this firm-based approach, rather than the traditional product-based approach, combined with leveraging real-world evidence, would create market incentives for greater investment in and growth of the digital health technology industry," he added. "Such processes could enable developers to deploy new or updated software more rapidly and would help FDA to better focus our resources."

The plan would come along just as FDA is set to benefit from additional user-fee resources to support digital-health reviews and, in particular, launch a new digital health unit within the device center. *(Also see "User-Fee Facts: 10 Key Medtech Details From US FDA Agreements" - Medtech Insight, 11 May, 2017.)*

AN FDA TURNAROUND?

Thompson says that since 2011, the CDS Coalition has been urging FDA to publish guidance to clarify the scope of its oversight of clinical decision support software and tackle other unresolved digital health issues. While even just a few months ago, the agency seemed unsure what to do in the area, the attorney noted, Gottlieb now appears to be accelerating forward.

"That is music to my ears," Thompson said. "Indeed, it seems that FDA is committed to going beyond just the technology addressed in the 21st Century Cures Act," he said. "Legislation always covers at best a few of the larger categories, and there is truly much more work to be done. Although it is not specifically addressed, we are very hopeful that the plan includes addressing software used in connection with pharmaceuticals."

As the agency develops guidance documents to implement the Cures Act, Thompson says he hopes FDA will look at the consensus guidelines that the coalition has developed on the transparency provisions in the legislation.

"Specifically, the coalition has been spearheading the development of guidelines for designing clinical decision support software to preserve the health-care professional's role in decision-making," said Thompson. "The guidelines address how to empower health-care professionals to be able to adequately review the basis of recommendations software makes."

Wade Ackerman, a partner at Covington & Burling, also lauded Gottlieb's push to reform the agency's regulation of digital health.

FDA Commissioner Scott Gottlieb

Ackerman previously served as senior FDA Counsel for the Senate HELP Committee, where he played a lead role in forming the software provisions and other sections of the Cure Act.

"While Congress addressed some aspects of FDA's regulation of health software in the 21st Century Cures Act last year, the digital landscape continues to evolve rapidly," Ackerman said. "FDA's intent to outline a new digital health innovation plan appears to recognize that developers across the life sciences, technology, and health-care sectors are finding new ways to harness the power of data and information technology to create cutting-edge innovations that will empower consumers and improve patient care."

Medical device lobby group AdvaMed, which recently created a new arm called AdvaMed Digital dedicated to representing digital health companies, says they are reviewing the plan and are looking forward to working with the agency on it.

"We are committed to working with FDA on ways to streamline review processes for digital health technologies that will maintain the agency's robust standard for safety and effectiveness while promoting the rapid innovation for which this sector is known," said Zach Rothstein, AdvaMed associate VP for technology and regulatory affairs.

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China's Venus Persists With Global TAVR Solutions Expansion

TINA TAN tina.tan@informa.com

Chinese transcatheter aortic valve technology specialist **Venus MedTech Inc.** is further expanding its product portfolio as well as its geographic presence with the acquisition of **InterValve Inc.**, a privately-held US developer of balloon aortic valvuloplasty products.

Financial details of the deal were not disclosed.

Minneapolis, Minnesota-based InterValve brings to Venus two products, the *V8* and the newer-generation *TAV8*, which have been US FDA-cleared and CE marked since 2013. Both products are designed to inflate and deflate rapidly to reduce the duration of obstruction across the valve and feature a "figure-8" shape balloon that enables the bulbs at either end of the balloon to lock into either side of the aortic annulus.

This design has the potential to reduce the risk of balloon movement during dilatation; it maintains the figure-8 shape throughout inflation which allows for leaflet hyper-extension, to create maximum valve area opening, without increasing the risk of over-stretching the annulus. The difference between the V8 and TAV8 is that the latter has reduced bulb lengths which allow for procedural improvements such as, among other things, decreasing the inflation/deflation time as there is 15-20% less inflation volume, according to InterValve's website.

The V8 catheter is designed for stand-alone balloon aortic valvuloplasty and pre-dilatation during TAVR procedures.

InterValve was founded in 2008 by Boston Scientific alumni Mark Ungs and William Drasler, and the company had enlisted **Getinge AB** as its exclusive US distributor in 2015. However, Venus stated in its press release that following the acquisition, it will be responsible for the global production and sales of V8 and TAV8.

The purchase of InterValve comes just over a year after Venus acquired the technology portfolio of German company **Transcatheter Technologies GMBH**. Transcatheter Technologies' had developed the *Trinity* TAVI system which is designed to be repositionable, even after full implantation. Trinity also features a novel sealing cuff to eliminate paravalvular leakage, a common complication of TAVI. The supra-annular positioning of the Trinity valve is also said to help reduce the risk of atrio-ventricular block.

Aside from these acquired technologies, Venus also has proprietary heart valves in its expanding portfolio: the *A-Valve* transcatheter aortic valve, which was approved by China FDA in April this year, and the *P-Valve* pulmonic valve, which is currently in clinical trials.

The Hangzhou-based company has also been looking beyond China to forge partnerships with other players in the interventional cardiology market. In September last year, it set up a joint venture – named **Colibri-Venus Medtech JV** – with US Frim **Colibri Heart Valve LLC** to help with the global commercialization of the A-Valve and the P-Valve. *(Also see "Colibri Enters TAVR Joint Venture With Venus Medtech Focusing On Emerging Markets" - Medtech Insight, 3 Oct, 2016.)*.

In February this year, Venus inked an agreement with Israeli firm **Keystone Heart Ltd.** to allow the Chinese company's TAVR system to be supplied in combination with Keystone's *TriGuard* cerebral embolic protection device, designed for use during TAVR procedures. This agreement covers China and key Asian markets alone.

Venus said its focus was to provide interventional cardiologists that are performing TAVR with solutions for the "holistic treatment of thrombus protection – balloon – valve", and not just the heart valve component only. This approach, according to the company, will offer "a systematic and comprehensive reduction of the risk of brain and annulus injury that might be caused by TAVR."

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Zimmer Biomet Resolves Chinese Plant Warning Letter

ELIZABETH ORR elizabeth.orr@informa.com

US FDA has resolved a warning letter issued to a Chinese **Zimmer Biomet Holdings Inc.** manufacturing facility in 2015, the company announced in a June 13 filing with the US Securities & Exchange Commission.

The June 3, 2015, warning letter to Zhejiang Biomet Medical Products Co. alleged multiple quality systems problems, several of which were related to the company's handling of nonconforming product. Specifically, FDA said the facility, which makes orthopedic surgical instruments used for knee prosthesis systems, didn't have proper procedures to control nonconforming product or identify the actions needed to correct and prevent recurrence of nonconforming product and other quality problems. Zhejiang Biomet also didn't monitor production processes to ensure devices met specifications, the letter states.

The May 8 closeout letter says the plant has addressed the violations found in 2015, but notes that future FDA inspections "will further assess the adequacy and sustainability of these corrections."

"The successful clearance of the Warning Letter related to our Zhejiang, China, manufacturing facility is a measure of the progress we have made in our ongoing quality and operational excellence journey," David Dvorak, Zimmer Biomet's president and CEO, said in a statement.

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Olympus Settles Power Morcellation Suit

ELIZABETH ORR elizabeth.orr@informa.com

Olympus Corp. and its subsidiaries have agreed to settle a lawsuit claiming the company's power morcellation tool spread cancerous tissue throughout a woman's pelvis and abdomen during an operation.

The suit, filed in 2015 by Georgia residents Elvis and Betty Dobson, was one of at least three morcellation-related suits against Olympus now pending in Philadelphia's Court of Common Pleas. Betty Dobson was diagnosed with cancer after she underwent a hysterectomy using Olympus's *PKS PlasmaSORD Bipolar Morcellator* in 2010.

The parties announced the settlement in a May 30 letter asking Judge John Milton Younge to dismiss the case.

Power morcellators break up uterine tissue into smaller pieces for removal through a laparoscopic incision in the abdomen. But if the tissue is cancerous, the procedure could inadvertently allow the malignant cells to disperse throughout the body. In 2014, US FDA warned against the use of morcellators in hysterectomy or uterine fibroid removal. *(Also see "FDA Warns Against Power Morcellators For Uterine Fibroid Surgery" - Medtech Insight, 17 Apr, 2014.)*

But Dobson claimed in the suit that Olympus should have been aware of the risks before FDA took action. Specifically, her complaint pointed to journal articles and patent office records from the mid-1990s that mentioned the potential for morcellators to spread diseased tissue. She argued that Olympus should have altered the design of power morcellators to reduce the known risk.

Olympus declined to reveal the financial terms of the settlement and said it did not represent an admission of guilt.

"Any claim against the company is unique and is addressed on an individual basis," spokesman Mark Miller said in a statement. "Settling any claim is not an admission of guilt but a recognition of the realities of a trial and the potential implications for the company. A reasonable settlement brings a more rapid and certain closure to this matter for all parties."

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Former ArthroCare CFO Pleads Guilty to Fraud

ELIZABETH ORR elizabeth.orr@informa.com

Former **ArthroCare Corp.** Chief Financial Officer Michael Gluk pleaded guilty to his part in a multimillion dollar securities fraud scheme June 14 in an Austin federal court.

In pleading guilty to one count of conspiracy to commit securities and wire fraud, Gluk is admitting that he helped to inflate ArthroCare's sales and ad revenue by manipulating distributor transactions. Gluk also confessed to having provided false testimony in proceedings before the SEC and in federal district court as part of the plea, the US Department of Justice said.

According to DoJ, ArthroCare regularly shipped more products than what customers had actually ordered, and then reported all shipped products as sales. This both allowed the firm to meet quarterly earnings forecasts and inflated ArthroCare's reported revenues by tens of millions of dollars.

Over the five years of the scheme, ArthroCare reportedly "parked" $37m worth of devices with the company's largest distributor, DiscoCare, Inc. In return, the distributor received substantial, upfront cash commissions, extended payment terms and the ability to return product, as well as other special conditions. ArthroCare then purchased DiscoCare in 2007 because the distributor owed ArthroCare a substantial amount of money on the unused inventory.

The plea further states that Gluk and his co-conspirators caused ArthroCare to file false statements with the US Securities & Exchange Commission in 2007 and 2008 that misrepresented ArthroCare's quarterly and annual sales, revenues, expenses and earnings. Following ArthroCare's July 21, 2008, announcement that the company would restate its recent financial results due to an internal investigation, ArthroCare's share price dropped from $40 to $23. The value later dropped to less than $6 per share.

Gluk resigned from ArthroCare in December 2008. His sentencing date is yet to be scheduled. A co-conspirator, former ArthroCare CEO Michael Baker, is scheduled to go to trial on Aug. 7.

Two other former ArthroCare execs, spine division head David Applegate and senior VP John Raffle, pleaded guilty to multiple felonies in 2013 for their role in the fraud. The company also agreed to pay a $30m fine to the DoJ in 2014. Further, the company, along with Baker and Gluk, settled an investor's class-action suit for $74m in 2011. *(Also see "Ex-ArthroCare Chiefs Convicted Of Orchestrating Fraud" - Medtech Insight, 4 Jun, 2014.)*

Smith & Nephew PLC paid $1.7b to acquire ArthroCare in 2014. *(Also see "Mega-Deals In Orthopedics: Size Matters" - Medtech Insight, 30 May, 2014.)*

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Positive Data Give DePuy Synthes' Attune Further Knee-Up

REED MILLER reed.miller@informa.com

New clinical data showing the stability and longevity of **DePuy Synthes** *Attune* knee replacement system's tibial base is the latest example of in the company's ongoing efforts to stockpile post-market clinical evidence supporting this flagship product.

DePuy Synthes, a Johnson & Johnson company, launched Attune in 2013. Attune was specifically designed to improve the stability and the motion of knee replacements compared to competing devices and improve patient's overall satisfaction with the operation.

"The incidence of knee osteoarthritis continues to increase, partly due to an aging population and due to a more obese population, so we saw that the number of individuals who need or will need a replacement will continue to grow," Torbjörn Sköld, VP – Joint Reconstruction, Sports Medicine, and Power Tools at DePuy Synthes for Eurupe, Middle East, and Africa, told *Medtech Insight*. "Although knee-replacement is recognized as among the most common successful surgical procedures, research indicates that 10% to 20% of knee-replacement patients are not completely satisfied with their operation. So we saw a huge unmet need."

The Attune knee system represents "the largest research and development project in the history of DePuy Synthes one of the largest evidence-generation programs that we have," he said. "We spent a significant amount of resources on R&D and we got renowned experts around the world to design Attune and now we're starting to have longer-term results."

In a 30-patient study by the Radiostereometric Analysis (RSA) Network of Canada, tiny tantalum beads were inserted into the bone surrounding the Attune implant at the time of surgery to serve as X-ray markers to detect changes in the position of the tibial base relative to the bone. Glen Richardson of Dalhousie University in Halifax, Nova Scotia, and colleagues presented the results as a poster at the Canadian Orthopaedic Association Annual Meeting, held June 15-18 in Ottawa.

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The radiostereometric data showed that Attune's tibial base migrated an average of 0.02 mm in the superior-inferior direction over two years, with an average maximum total point motion of 0.21 mm and the average micromotion – the small movements between the tibial component and the bone – was 0.17 mm between the one- and two-year follow-up. Based on published criteria used to predict future revision rates based on RSA data, these results show Attune achieved stable fixation and will have acceptable revision rates due to aseptic loosening, according to DePuy Synthes.

"These results are another component of the breadth of data that continue to be generated around the ATTUNE Knee," Kim Dwyer, the Clinical Research Director for Knees in DePuy Synthes Joint Reconstruction division said. "The importance of RSA is that it can help predict an implant's long-term performance while larger and longer survivorship studies are underway."

A few weeks earlier at the European Federation of the National Associations of Orthopedics and Traumatology Congress in Vienna, DePuy Synthes announced the four-year survivorship data UK's National Joint Registry, an independent organization collecting data from joint implants from all manufacturers implanted throughout the UK except in Scotland.

These results show that only 46 of the 10,605 Attune knees in the registry's database required revision surgery and the cumulative revision rate for Attune Knee was 1.3% at four years, which is equivalent to a 98.7% implant survivorship. This compares favorably to the 1.9% cumulative revision rate (98.1% implant survivorship at four years) for the overall class of total knee replacements in the registry.

A separate analysis showed that based on historical data for total knee replacements and duration of implantation, age group, gender, and indications, the expected number of revisions in the Attune patients in this registry would be 63, so that the actual revision rate beat the expected rate by a statistically significant margin.

Josh Paul Bridgens, DePuy Synthes' Medical Director for Joint Reconstruction and Power Tools for Europe, the Middle East, and Africa, told *Medtech Insight* this is the first data on four-year survivorship with Attune. "That was something we wanted to let surgeons know about as soon as possible, because although

Attune wasn't designed to address survivorship – because it is already good – it's the kind of absolute [metric] surgeons want to know about. And there are some markets, particularly in Europe, where they won't use a joint replacement until they have three or five year's survivorship [data]."

The four-year data from the National Joint Registry also include patient reported outcomes measures showing that the percentages of patients reporting excellent or very good outcomes with Attune is significantly higher than percentages for all knee-replacement patients in the registry.

Sköld highlighted a few features of Attune that might be the most responsible for these encouraging outcomes. The *Gradius Curve*, the curvature of the femoral component of the implant, is a patented "gradually reducing radius" designed to reduce "unnatural sliding of the femur on the tibia." He also mentioned the *Glideright* articulation, a patented design to accommodate variation in patient anatomy and soft-tissue interaction, while optimizing the tracking of the patella and reducing anterior pain that some knee replacement patients experience.

Attune also features the *Logiclock* tibial base to reduce wear and optimize kinematics, and is sold with the *Intuition* lightweight surgical instruments which are specifically designed to implant Attune.

PART OF THE PLAN FROM THE BEGINNING

"Attune is the biggest evidence-generation program we've ever put in place and – this might be commonplace now but wasn't a decade ago [when we started] – it was part of the Attune project right from the start," Bridgens said.

In addition to the in-vitro and premarket clinical evidence, DePuy Synthes has been committed to developing the "value" evidence for Attune. About 1,200 patients from 20 centers worldwide have been implanted in trials sponsored and initiated by the company to study the functional results with Attune. The company is also sponsoring trials initiated by investigators. "They tend to be more 'bespoke' kinds of studies, maybe looking at the kinematics of the joint and we have a number of RSA studies ongoing, which are producing results as well and looking at very accurate assessment of early fixation of the device."

The company is also collecting data from worldwide registries. "The use of those was part of this evidence plan right from the start. They do have some unique advantages compared to all of the other things I described already," Bridgens said. "One of the great things about registries is just the number of patients and implantations you get within them." In addition to the National Joint Registry in the UK, data on Attune is being collected in registries in Australia, New Zealand, and Germany.

"The other reason registries are important is that no matter how we do our studies, there's always going to be some degree of question of them because they're funded by us. So the registries have the benefit of being completely independent," he said. "They also are looking at the entirety of use of the implant in a country or in a region. This just isn't us picking the best surgeons and getting them to put in our implant, this is absolutely everyone using it and looking at the results."

Sköld said the company is continuing to build upon the Attune technology platform. The first extension of the Attune product line is the *Attune Revision Fixed Bearing Tibial Base* and the 14x50 mm *Attune Cemented Stem*, both launched at the American Academy of Orthopedic Surgeons annual meeting in San Diego in April. These expansions of the Attune line address complex primary knee replacements and partial revisions of previously implanted Attune knee joints.

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business will account for roughly 40% of total revenue.

Brandon Couillard, analyst at Jefferies, noted that the purchase price was over four times that of EUROIMMUN's expected revenue, "a somewhat rich multiple, but reasonable given its growth prospects and strategy fit."

The acquisition, which only requires German and Chinese anti-trust approval, is expected to close in the fourth quarter of 2017, will not impact PerkinElmer's revenue and earnings per share guidance for 2017, but will be accretive to its 2018 non-GAAP EPS by around $0.28-$0.30.

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LONDON TECH WEEK:

Asthma Sensors, Smartphone Health Monitoring & Eczema Management Garments

CATHERINE LONGWORTH catherine.longworth@informa.com

Growthdeck, an online equity crowdfunding platform, hosted a special investor event during London's Tech Week to put the spotlight on emerging UK medtech companies.

The UK medtech sector has experienced growth in recent years. A 2016 annual report published by the European Patent Office showed the UK saw a 22.4% rise in the number of medtech patent filings and reported that medtech was the second strongest sector for European patent filings, behind transport. *(Also see "Philips Tops EU List As Most Prolific Medtech Patent Filer In 2016" - Medtech Insight, 10 Mar, 2017.)*

Three early-stage medtech businesses currently seeking investment were showcased at Growthdeck's Tech Week event: **Redecol**, an asthma monitoring device company; **Bioepic**, which is turning smartphone cameras into non-invasive vital signs monitors; and **iFabric**, which manufacturers of a proprietary polymer for eczema and dermatitis management.

The evening session opened with a talk from medtech entrepreneur Graham Hine, the former CEO of companies including **Capteur Sensors**, **Microsaic**, **P2i**, **Hardide** and **SGX Sensortech**. Hines told the audience that medtech remained a hot sector, with technologies for improving aging and chronic diseases providing the best opportunities for investors. "The focus in the industry now is on prevention rather than treatment," Hines said. He advised potential investors to judge medtech companies by the strength of the CEO and their team, as well as on whether the technology would have a sustainable competitive advantage in its market and improve patient outcomes.

MEDTECH STARTUP PITCHES

Asthma monitoring start-up **Redecol** was founded in February 2017 and is targeting 2020 for a market launch of its *BreatheEasy* lung-monitoring device. BreatheEasy does not require the forced breathing technique currently required by peak flow meters and only needs the patient to deliver controlled breaths to show if lung function is stable or deteriorating, Redecol says. The device automatically records the results and plots trends so it can provide early warnings to sufferers when their symptoms begin to worsen. It can also be linked to smartphones and results sent to healthcare professionals if further advice is needed.

The company, which was formed from a vendor-assisted management buy-out from Anaxsys Ltd, said it is seeking £750,000 from investors for 43% equity. Tim Coutts, Redecol CEO said the funds would be used to continue development and commercialization of BreatheEasy. Redecol also has two further trials planned in 2017 - a 20 patient clinical challenge study at Leicester University Hospital and a 100 patient comparator study in India, which is due for completion in Q3 2017.

Bioepic is seeking funds to roll out its smartphone camera monitoring technology for measuring vital signs. The technology uses smartphone camera sensors and flash capabilities to take a photoplethysmography (PPG) stream from the user's fingerprint and reconstruct a pulse that represents their prototype pulse. This information is then analyzed to identify prominent characteristics and calculate the range of indexes related to the cardiovascular system performance using processing tools, statistical patterns and heuristic techniques. Bioepic CEO, Dominic Wood, said the company is raising £500,000 for investors to acquire a 12.5% equity share in the company. Its existing investors include the company founders and one of the UK's largest occupational health providers as well, as the founder of Sofa.com and the Head of Innovation at **Roche Pharma AG**.

The final pitch of the event came from **Intelligent Fabric Technologies** which manufactures silk garments for sufferers of eczema and dermatitis. The specialist garments are treated with the company's *DreamSkin* proprietary polymer, which is designed to protect the skin from external irritants. "It's based on the same technology used for contact lenses," explained iFabric founder & CEO George Costa.

The polymer is applied to fabric by ionic coupling to create a bond between fibres and the polymer. During the drying process, the molecules form into a multi-layer lamella structure which creates a strong hydrophobic and hydrophilic barrier that protects against irritants and retains moisture. The garments also contain a class-leading zinc-based antibacterial which provide control of bacteria within the garment.

iFabric is seeking £1m to bring the technology to the primary care market. "We want to raise the profile of this technology and the primary care market is the biggest opportunity for us," said Costa. The company's range includes 85 different clothing garments which have been approved by the UK MHRA and the US FDA.

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As Device Firms Take Costa Rica By Storm, Quality Control Experts Champion 'Pura Vida'

SHAWN M. SCHMITT shawn.schmitt@informa.com

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"Sometimes companies have issues – they'll say, 'I don't know how to do this thing' – so we cooperate with each other and help," Medtronic's Martin Camacho Grünwedl says.

When Costa Rican quality assurance experts Martin Camacho Grünwedl, María Celina Corrales and Vanessa Rivel need a helping hand to understand, say, a complex standard, or they're stumped by a burning compliance, quality or regulatory issue, they know exactly where to turn: to each other.

Despite being employed by three different medical device firms with facilities in the country – Grünwedl from Medtronic, Corrales from Creganna Medical, and Rivel from Precision Concepts – they periodically meet, along with other QA managers and professionals from an array of other firms, to find sought-after answers and much-needed support.

Costa Ricans "like to do things the right way," said Rivel, Precision Concepts' quality systems & regulatory compliance manager. "When we have quality problems, we really do try to solve them and not to hide them. When there are defects in the manufacturing lines, we try to address them, to solve them, and not sweep them under the rug.

"That, of course, generates confidence in our businesses," she added. "We all win when we learn together."

Grünwedl, a Medtronic senior quality manager, chimed in: "For example, all of us need to comply with the new 2016 version of ISO 13485. We all know we need some training on that. Or there might be topics from [US] FDA we need to know about – we get together and talk about those new things, if there's some new approach from the FDA. So, we're all learning together about those types of things, and we support each other."

Companies use international quality standard ISO 13485 to ensure quality systems compliance with regulators in different countries, including Canada, Japan, Australia and the 28 member-states of the European Union. The standard's requirements for device manufacturers are similar – but not identical – to FDA's Quality System Regulation.

During other intercompany powwows, "we talk about, for example, CAPAs [corrective and preventive actions] and CAPA investigations, or we'll discuss the importance of good writing and to be prepared for that," Grünwedl said.

When it came to learning better writing techniques, "there was one company that was looking for that training, so we all got together to have one training for all of us at the same time," he said. Grünwedl pointed out that the meetings – held every two or three months by an organization known as CINDE – "is also for people to improve their technical knowledge on quality and the different tools we need."

Founded in 1982, CINDE is the Costa Rican Investment and Trade Development Board. A nonprofit, private entity with no political ties, it serves to promote the country and attract foreign investment.

Medtech Insight spoke with Grünwedl, Rivel and Corrales on June 1 at an industry educational conference on process validation and risk management in San Jose, Costa Rica, hosted by the Biomedical Division of the American Society for Quality. With strong support from local device-makers, CINDE lobbied to bring the ASQ meeting to Costa Rica, which took about two years to plan and take shape.

Several companies "had been talking for a long time that it was important to have this process validation meeting in Costa Rica," Grünwedl said. "Process validation is one potentially difficult topic that is com-

mon between the companies, and we talked about how we needed experts here in Costa Rica teaching us about these things.

"Sometimes companies have issues – they'll say, 'I don't know how to do this thing' – so we cooperate with each other and help," he noted.

That level of collaboration between companies may sound overly warm and fuzzy to American, Asian or European ears, where device firm employees are more cautious when engaging with their peers from different companies, even when in a cordial professional setting such as a medtech conference.

But in Costa Rica, "Pura Vida" rules. The Spanish phrase that means the "pure" or "simple life" isn't just the unofficial motto of the country; rather, it's a state of mind, locals say. Helping each other for the greater good is something that is woven into the fabric of the nation and its people.

Nevertheless, that doesn't mean QA experts become overly chummy with their counterparts at potentially competing firms.

"At our meetings, when we talk about issues firms are having, we're not necessarily talking about specific issues that a specific company is having. Rather, it's overarching training; for instance, how should you approach a CAPA?" said Corrales, Creganna Medical's senior quality manager. "Of course, we're not going to share confidential information."

WHY COSTA RICA?

Support amongst peers is needed now more than ever because the country is in the midst of a device manufacturing boom. It may be surprising to some that medical devices are Costa Rica's No. 1 export, and the country is the No. 2 exporter of devices in Latin America.

According to CINDE, exports of devices grew at an average annual rate of 14.3% between 2005 and 2015 (from $580m in sales in '05 to $2.2bn in '15). This growth was likely one factor that led FDA to open a field office in San Jose in 2009. *(Also see "US FDA opens offices in Latin America and Europe" - Medtech Insight, 5 Feb, 2009.)*

Everything from high-risk class III devices to low-risk class I's are made in Costa Rica, including medication delivery systems, intravenous pumps, bovine heart valves, and surgical and diagnostic instruments. Baxter was the first international firm to settle in the country, opening its doors in 1988.

Medical devices are Costa Rica's No. 1 export, and the country is the No. 2 exporter of devices in Latin America.

The number of companies that have opened manufacturing facilities there has more than doubled over the past decade or so. Data from CINDE shows that 68 firms – from giants such as Medtronic, Boston Scientific and Covidien, to smaller ones like Precision Concepts and Creganna Medical – crank out product here, mostly in San Jose's outlying areas of Alajuela and Heredia.

Moving facilities to Costa Rica makes sense for some firms, especially those based in the US, because it's cheaper to make product and pay wages, and because it's convenient for doing business – the country is roughly only a five-hour flight from most Gulf Coast states and Costa Rica shares the United States' Mountain Time Zone.

"We are very close to the States. It's the biggest market of medical devices in the world right now, and because we're in the [Mountain Time Zone], it's very easy to communicate with headquarters," said Creganna Medical's Corrales, whose firm makes medical balloons, and metal and braided shafts, among other products.

Medtronic's Grünwedl believes it's the Costa Rican people who make moving manufacturing sites to the country even more attractive.

"We have very good, educated people here. They know English. It's part of the education," he said. "We abolished the army here, so all of that money is vested in education. Also, people here are very interested in technology."

Costa Rica's military was disbanded in 1948 following civil war.

"I believe the people here are very passionate. That doesn't mean we want to do things right and people in other countries don't want to do things right," Grünwedl said. "But Costa Ricans are very passionate to make things happen, to solve the issues – to make things different. We love challenges, so if we have a challenge, that's something that motivates us to do things to raise the bar. I believe that, based on that, we are having a very good reputation right now regarding audits and inspections.

"We don't have too many quality issues at the companies here. That's also something that is very attractive for the companies that are investing here."

To help meet the demand in manpower at device firms, local universities have incorporated studies in quality and regulatory geared toward medtech manufacturing.

"Locally, we are looking to have quality technicians ready – to know the statistics, to know about quality and quality tools," Grünwedl said. "That's something we're managing with universities here. They include programs for quality, manufacturing supervising, English – that's a big topic at the universities. And there's microbiology mixed with some engineering. These are new programs to align to the needs of the medical device industry."

For example, Tecnológico de Costa Rica in Cartago offers degrees in medical device engineering, while Universidad Técnica Nacional, with campuses situated around the San Jose area, offers a diploma

Coocoo For Costa Rica

Since the mid-2000s, ever-larger manufacturers have been making the leap to Costa Rica, sometimes shuttering facilities in the US. Here's a selection of *Medtech Insight* reports tracking the rise of device-making in the country:

- **2005:** "Hospira has announced it is to shut down its medical device manufacturing plant in Donegal, Ireland. Production at the Donegal site will be transferred to the company's other facilities in Costa Rica and the Dominican Republic." *(Also see "Hospira closes Irish factory, over 500 jobs axed" - Medtech Insight, 9 Sep, 2005.)*
- **2011:** "Boston Scientific has indicated that it will cut 167 jobs at a manufacturing facility in Doral, Fla. The redundancies are part of an ongoing plan to relocate the Doral operation to Alajuela, Costa Rica, first disclosed in November 2009." [In 2015, Boston Scientific moved the production of many of its electrophysiology products from Northern California to Costa Rica.] *(Also see "Boston to make more redundancies as part of Costa Rica move" - Medtech Insight, 25 Jul, 2011.)*
- **2011:** "Among other site location trends … is the emergence of Costa Rica as the epicenter of the Latin American medical device industry over the last 10 years. More than 50 device firms currently operate facilities there, including St. Jude Medical, Allergan, Boston Scientific and Abbott Vascular. Key draws of Costa Rica include the country's high literacy rates, labor-training programs, green hydroelectric power, free-trade zone industrial parks and the Panama Canal's upcoming expansion." *(Also see "Coastal States Among Most Costly Device Manufacturing Locales – Report" - Medtech Insight, 11 Apr, 2011.)*
- **2012:** "Covidien is the latest medtech company to join the workforce cull as it plans to cut 595 full-time jobs with the closure of a facility in South Carolina. The closure is part of the company's plan to cut costs amid challenges brought on by pricing pressures and reimbursement issues. The closure of the Seneca facility is expected to be completed in three years and its operations will be transferred to another plant in Alajuela, Costa Rica." *(Also see "Covidien adds to medtech layoff toll with 600 job cuts" - Medtech Insight, 14 Sep, 2012.)*
- **2013:** "'For the first time in our 25-year history … we've been forced to look at manufacturing outside the US,' Cyberonics CEO Dan Moore said. 'It's primarily driven, first, by overregulation, and the second piece is the tax.' Until now, Cyberonics has done all of its manufacturing at its Houston-based headquarters. But recently, the firm broke ground on a manufacturing plant in Costa Rica. 'Every job that we put in Costa Rica is a job that we're not going to put here,'" Moore said. *(Also see "MDMA Will Focus On FDA Performance, Device Tax Repeal In 2013" - Medtech Insight, 4 Feb, 2013.)*
- **2014:** "Volcano says it plans a limited market release of the low-profile *Phoenix* system by the end of the year and a full launch in early 2015. The company will initially manufacture the device at AtheroMed's Menlo Park, Calif., facilities, but it will transition to Volcano's manufacturing site in Costa Rica by next year." *(Also see "Volcano Cuts Deeper Into Peripheral Market With AtheroMed Buy" - Medtech Insight, 28 May, 2014.)*

in quality control, as well as a bachelor's program in process and quality.

UTN also boasts a Center for Productivity and Quality. Launched in 2008, the center "provides consulting, advisory, technical assistance and training services focused on improving the productivity and quality of companies," the school says.

'INTÉGRATE A COYOL' TRAINS QUALITY TECHNICIANS

Despite the educational opportunities presented by Costa Rica's more traditional universities, Medtronic's Grünwedl and Creganna Medical's Corrales say their biggest quality challenge is finding people with adequate education and experience.

Manufacturers "need a person in quality who knows about suppliers, compliance, operations, and such. It's not easy to get those types of people," Grünwedl said. "Some people will know, say, about validation activities, but not so much about operations, for example. Trying to maintain quality assurance people is difficult."

Device-makers must also deal with competitors poaching employees.

"It's difficult because more and more firms are coming to Costa Rica. There's competition to attract the right people, and it's getting worse," Corrales said. "Some people don't like the little device company they're in, so they jump to another one. Many companies are located close to each other. They just need to cross the street and go to another company. You can lose good people very easily."

To help meet the growing needs of the device industry, a program was designed by the Coyol Free Zone to train locals on the basics of becoming a quality technician.

The Coyol Free Zone, located in Alajuela, is Central America's largest business park. Hologic, a maker of diagnostic products, medical imaging systems and surgical products, was the park's anchor tenant when ground broke on the complex in 2007. The CFZ is now home to scores of device firms, including St. Jude Medical, Volcano, Abbott Vascular and Moog, to name a few.

The four-week long "Intégrate a Coyol" training program educates recruits on regulatory and quality issues, biosafety, asepsis, management of cold rooms, and

technicalities in English, among other topics. Launched in 2016, the program is extremely popular amongst device manufacturers in the CFZ.

Intégrate a Coyol is "based on our need to train people from our influence zone so they become skilled candidates with the capabilities that businesses search for when it's time to recruit operative staff," María José Crespo, a service manager for CFZ, told Costa Rica's Canal 3 TV in March.

The program offers "subjects about the industry's employability; subjects about quality; subjects about production," she said. Recruits "need to understand all of the terminology that they are going to encounter when they work in [the device] industry."

Trainees also learn about work responsibilities and values, as well as occupational health.

"What we offer to people is to train them, to prepare them so they have all of the fundamentals, so when they have to face an interview or a recruitment process for a business, they already have a very big part of the process covered and have gained the knowledge to be a suitable candidate with the capabilities and the qualities that the businesses search for," Crespo explained.

At Precision Concepts, which is a finished device manufacturer, quality technicians trained through Intégrate a Coyol are welcomed with open arms.

That's because "they know some basics around GMPs, how to enter the clean room, sterilization, and some other basics that operators need to know," Rivel said. This helps to bridge the gap "between the requirements of the medical device industry and the knowledge of some of the population that live around the [Coyol Free Zone]."

Grünwedl agreed. Students "learn how to behave in a controlled environment, and learn good documentation practices. Those things are very basic, but sometimes for untrained people it's very hard. They'll want to know, 'Why is documentation important? Why do I need to write this? Why do I need to sign like this?' So Intégrate a Coyol is a solution for those people to get involved and be ready if they are hired in the medical device industry."

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German Medtechs Aim To Score Useful Points In 2017 Election Year

ASHLEY YEO ashley.yeo@informa.com


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Health-care costs, quality and coverage – and even regulatory processes, market access issues and safe use of products – are never far from the surface in Germany, whose insurance-funded system of health-care delivery is routinely dissected and debated in public forums. Members or Parliament in Germany (Abgeordnete) are frequently held to account on health-care technology issues in a way that doesn't always happen elsewhere in the EU.

With the German national elections just over three months away, Christian Democrat/Christian Socialist Union health policy representative Maria Michalk spoke at a gathering convened by BVMed, Germany's medtech industry association, about how things could change after the election. The CDU/CSU (center-right party) has been in power – albeit latterly shared with the FDP (center) and SDP (center-left) – for 12 years. Another term is starting to look more likely, according to the latest polls. (*See box.*)

Michalk says she supports the device industry's efforts to bring products to patients rapidly, but, she stressed, "the quality of the process must be appropriate." Michalk, however, was clear on one thing during the BVMed gathering in Berlin: market access processes that take seven years before a product can get into general circulation are too long, and politicians need to address that. *(Also see "Industry Sees Much To Improve In Germany's New High-Risk Medtech Assessment Scheme" - Medtech Insight, 11 Apr, 2017.)*

As the current legislative 2013-17 period winds down, Michalk claimed that the coalition agreement devised by health minister Hermann Gröhe four years ago has been fulfilled in its entirety. *(Also see "Germany's DRGs, innovation fund stand out in new govt plans" - Medtech Insight, 29 Nov, 2013.)* In the next period, digitalization of the health system will need to be the focus, in spite of fears that the system is not fully ready to embrace the IT opportunities in full. "We need to be courageous, or else events will overtake us," says c

She was also clear that if Germany's self-governing health-care system, composed of the units that run and organize health-care delivery, prevaricates over digitalization, then the government, which normally only sets the conditions for medical care, must take a lead. Pointing to potential governance and privacy concerns, she says patients must be in control of their own data, but the opportunities that IT would provide, even for basic needs such as the avoidance of repeated examinations, must be seized.

SICKNESS FUNDS OPTIONS

The CDU/CSU is in favor of keeping the dual system, whereby operating health-care costs are paid for via the sickness funds insurance system and capital equipment costs are paid via the federal states. The party is also determined to retain the public and private (GKV and PKV) insurance fund structure. It is not in favor of ideas circulated by the SPD, Left Party (Die Linke) and Green Party (Bündnis 90/Die Grünen) for a "citizen insurance" system, fearing it would lead to a two-tier system of medicine.

June 8 Poll Numbers

The CDU/CSU has seen a resurgence in popularity in recent weeks, while the SPD, led by new leader Martin Schulz, has seen its approval ratings fall, according to an Infratest-dimap opinion poll published June 8. After a dip in approval ratings when she opened the door to 900,000 asylum seekers, Chancellor Angela Merkel is now back up to a 64% approval rating.

The CDU/CSU is up 1%, to 38% approval, and the SPD down 3%, to 24%. The rest of the field is led by the Liberal FDP, with a 12% positive rating, up 2%. The Green Party, Die Linke (the Left Party) and the AfD anti-immigrant party have all lost ground.

The health system must be affordable, which means a CDU-led government would be looking to set new health-care delivery and structure laws, and improve cross-sectoral care within the in- and outpatient and rehab sectors, Michalk said.

Germany's health-care sector generated revenues of some €337bn ($377bn) in 2016, corresponding to 12% of GDP, according to a WifOR economic research institute report, commissioned by the ministry of the economy.

10-POINT PLAN FROM MEDTECH INDUSTRY

The medtech industry has put together a ten-point wish list that it wants the new German government to act on, calling for:

- A renewed "innovation culture" and a positive atmosphere for medical-technical breakthroughs, appropriate reimbursement systems and a law on accelerated access to advanced technologies.
- Better representation for the medtech industry on the committees of the self-governing bodies, including the G-BA (reimbursement authority) and its IQWiG executive arm, where pharma and medtech "should carry equally-weighted representation."
- A properly-targeted benefit-assessment system for high-risk medtech products, the use of registry data in the provision of real-world evidence, a shorter evaluation period, the costs to industry calculated and notified in advance, and the participation of companies in the evaluation process.
- Transparency and accountability of DRG costings by InEK (the DRG's institute).
- Improved processes when medtech products used in the inpatient setting are also moved to the outpatient setting – and a quicker attribution of numbers for the EBM outpatient products reimbursement catalogue.
- Joined up and comprehensive hygiene measures to combat hospital-acquired infections. These measures should be paid from a separate reimbursement fund, and products that actively counter surgical site infections should be promoted actively.
- Medical technical aids used outside the inpatient setting should be bought based on quality, not price. There should be a federal-wide and transparent mechanism for the oversight of these contracts.
- Standardized care structures for chronic wound care, possibly via a Disease Management Program (DMP) with manufacturers' expert input.
- Building out a digital infrastructure for medtech. Proper reimbursement is yet to come, and when it does, it must be for systems that are interoperable. Regulations for medical or therapeutic mobile apps must be adapted from tried-and-tested medtech regulations.
- A task force in Germany for the practical application and understanding of the EU Medical Device Regulation (MDR) – especially for the benefit of small companies. Once Unique Device Identifiers arrive in the EU, medical institutions must be bound by it and must use it. And Health Technology Assessment (HTA) should remain a national – not EU – issue, as it cannot be separated from national reimbursement systems.

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How Soon Will New Eudamed Database Be Ready? What Are The Hurdles?

AMANDA MAXWELL amanda.maxwell@informa.com

Transparency is at the heart of the new Medical Device and IVD Regulations, and the new version of the Eudamed medical device database, with its seven separate but interlinking sections, will be a critical factor in creating this transparency and in providing regulators with the means of ensuring that only safe and compliant devices are circulating on the EU market.

But that requires the revamped database to be ready to operate in alignment with the transition to full application of the new regulations – 2020 for the MDR and 2022 for the IVDR. History has shown, and not only in the medtech sector, that building such databases is complex and slow.

While the EU MDR includes a provision to respond to a delay in the availability of the database, the system will work much more smoothly if the new Eudamed is ready on time. The volume and complexity of questions that arise if it is not ready on time will make already complex matters even more challenging and costly.

So how is progress going in developing the new database and what are the opportunities and challenges that will come from it? Medtech Insight asked Ronald Boumans, a senior global regulatory consultant at Emergo who has deep experience with the database.

Boumans was involved in the development of the original Eudamed database when he was a senior inspector at the Dutch competent authority, and he is on the steering committee for developing the latest version. In this interview, he discusses how the database is shaping up, what the timetable is looking like, and what challenges and potential destabilizing forces could lie ahead.

Medtech Insight: Are the deadlines for establishing the new Eudamed outlined in the MDR and IVDR tenable?

Ronald Boumans: It is an ambitious project and the functioning of the regulations depends on it. It appears the [European] Commission understands this and the Eudamed team have sufficient funds and mandates. Whether this will be enough can only be evaluated on hindsight. In case of delays in the development of Eudamed, Article 123(d) [of the MDR] provides a delay for the introduction of the Eudamed-related requirements.

It is also worth noting that the timetable has been developed in the context of the MDR. Once the system works for medical devices, it will also work for IVDs. Therefore, the timing of setting up Eudamed for the IVDs is not considered a critical issue.

What is the timetable? And what are the next steps?

Boumans: The working groups will have all started soon and their results will consist of definitions of data fields, their relation and the processes for entering data in these fields.

The functional specifications are expected to be ready in May 2018. In August 2019, the audit is planned, together with the consultation with the Medical Device Coordination Group which will support the Commission in signing off Eudamed as fit for purpose.

If all goes well, Eudamed may "go live" in August 2019, but not later than March 2020.

The process is more dynamic at the working group level. It is expected that later this year beta-testers will be able try out draft modules and procedures. These user tests will continue throughout the development of Eudamed.

You have been involved with Eudamed for over a decade, including during the setting up of the original Eudamed database. Can you explain your involvement?

Boumans: In 2006, I was working as a senior inspector for the IGZ, the competent authority for medical devices in the Netherlands. I was asked to represent the IGZ in the development team of the first generation of Eudamed. This version was introduced in 2010 (see Commission Decision 2010/227/EU) and Eudamed 1 had

to be fully implemented in 2012. This version was only open to the member states and the European Commission.

Can you explain what can be learned from previous experience, in your view, and what are some likely improvements in the forthcoming version of the database?

Boumans: Due to the fact that the individual member states were made responsible for entering data in the original Eudamed, there were differences in data quality. This led to entries being duplicated, to mistakes and missing data. An attempt to repair this was made by Eudamed 2, when the original Eudamed was upgraded, but that never really took off as the new MDR Eudamed was announced in the drafts of the MDR.

The new MDR Eudamed will be open to stakeholders and the general public, each with their own level of access. But the most important change, in my view, is that economic operators are made responsible for their own data. This will help increase data quality, which in turn can make Eudamed the backbone of market surveillance by the member states.

In the new Eudamed, each economic operator will be identified by a Single Registration Number (SRN) and each device will be identified by its Unique Device Identification (UDI). This will now enable unambiguous identification of who and what in vigilance cases and corrective or preventive actions.

Can you describe the current working structure in Europe that is developing the new Eudamed database?

Boumans: Eudamed is being developed by a team within DG GROWTH, [one of the Directorate-General's] of the European Commission. DG GROWTH has set up the Eudamed Steering Committee and working groups. The steering committee represents several stakeholders, including the member states. The steering committee evaluates results from the working groups and guards over the general concept of Eudamed. The working groups focus on the seven Eudamed pillars as well as certain common aspects: registration of economic operators; UDI; notified bodies and certificates; clinical investigations; vigilance; market surveillance; and data exchange.

What is your role in helping develop the new Eudamed?

Boumans: I am active on the steering committee, as well as the working groups for UDI, Vigilance and Data Exchange, where I represent the interests and expertise of the European Association of Authorized Representatives (EAAR).

However, I don't see my role restricted to representing the interests of EAAR. The typical client of an independent authorized representatives is a small or medium sized organization so the work I am doing will also help such organizations.

Who will be responsible for running the database?

Boumans: The database will be run by the European Commission on Luxembourg servers. However, all economic operators, notified bodies and member states will each be responsible for their own data. As part of the continuous market surveillance, the member states and the commission with oversee the data consistency within each economic operator as well as between economic operators for each UDI. It is expected that Eudamed will be quite volatile.

How will funding work? Why is there concern over fees?

Boumans: Eudamed will be funded by the European Commission and entering data can be done for free.

However, member states may levy fees based on Eudamed registrations. This is practically feasible if this concerns a reasonable fee for an economic operator in the member state where he, or his authorized representative, has his legal base.

But it appears some member states also want to introduce fees for devices that are distributed on their territory and they want to use Eudamed as the source of that information.

In my view, this goes against the principle of free movement of products on the single market, because it could, for example, limit the activities of a distributor in one member-state distributing to another. But I see a more serious risk: Eudamed is not intended for collecting that type of fee. Introducing such additional features is way out of scope of the intentions of Eudamed. Manufacturers may be cautious with entering data regarding their market coverage, which may lead to unnecessary delays in case of corrective actions. In my view, member states should first demonstrate the risk-to-benefit ratio of such a measure is acceptable.

What has been achieved and agreed so far, on a high level?

Boumans: The developing staff and the working groups have done a lot of work already. For many requirements in the regulations, the data fields and their relations have been established. Processes have been summarized in flowcharts. In general terms, entering data into Eudamed will follow this template [Editors' note: The working groups handling each of these fields are listed in brackets]:

An economic operator requests a Single Registration Number (SRN) and organizes authorization within his organization. The member state where he or his authorized representative has his legal basis must issue the SRN. In the case of non-European manufacturers, their authorized representative must confirm the mandate before the manufacturer can enter further data into Eudamed [Registration Working Group].

Next, the manufacturer can enter data into the UDI database about the device [UDI working group]. For notified body certified devices, the certificates must be confirmed and upload-

ed by the notified body. There are still some issues with this point, because some certificates cover hundreds or even thousands of devices [Notified Body and Certificates working group].

The working group on data exchange has just started and one of their highest priorities is to make sure a machine-to-machine interface is built into the system. This will enable automatic uploads and downloads of large quantities of data, without human interference. The working groups on clinical investigations, vigilance and market surveillance will start later this year.

Which delegated and implementing acts are needed to help provide the necessary structure?

Boumans: Currently, the Commission expects one delegated act for Eudamed. Although it should have a high priority, there are no indications this is being developed. On the upside, the regulations have many Eudamed-related requirements already listed. Most of the work can therefore be done now, and a delay in the delegated act may even be an opportunity to add results of the Eudamed development into that act.

I hear there are some concerns relating to nomenclature. Can you please explain?

Boumans: It is obvious that one of the preconditions for Eudamed is the availability of a single devices' nomenclature that all operators will use. Article 26 is about the European Commission making available internationally recognized medical devices' nomenclature free of charge but it is not certain which nomenclature that will be and how this will be organized.

What are the other likely biggest hurdles?

Boumans: There are several issues which have the potential of sabotaging Eudamed.

Firstly, there is the problem with the certificates. It appears sensible to consider an electronic document equivalent to a certificate, but there are legal reasons to require a hard copy with a real signature. The times of parchment rolls being distributed by mail coach are long past, but there still are some strong arguments to stick with hard copies. In my view, this is an opportunity to introduce some 21st century procedures into our legal system.

> "Scope creep is another risk. Some member states are also trying to build supervision activities into Eudamed."

Scope creep is another risk. Some member states are also trying to build supervision activities into Eudamed. That may not look like a big deal, as Eudamed is intended to support supervision. But the moment this leads to an extra burden for the economic operators entering data, and a higher regulatory risk, it may reduce compliance to the system and thereby reduce the efficacy of Eudamed. As said before, for these measures the benefits must clearly outweigh the risks.

A third risk is not directly linked to Eudamed and concerns the member states that have to issue the SRNs. With about 70,000 SRNs expected in total and with an estimated two hours for each SRN (which in my view is a very optimistic estimate) member states will be looking at 140,000 working hours to be spent in 2019 and 2020. That means about 5,000 hours on average, per member state, which would translate into four people [working] full time. So far, I have not seen any evidence that member states are preparing for this. By not acting now, they threaten to create an unnecessary bottleneck that is not covered by the exemption of [MDR] Article 123.

Last but not least, there is, of course, the unknown risk. The Third Law of Project Dynamics predicts that it always takes longer than you think, even if you consider the Third Law of Project Dynamics.

That will inevitably be the case for Eudamed too. We should stay vigilant for the moments these unknown risks manifest themselves and be ready to act. That is something the medical device industry has experience with, and, hopefully, the authorities will also take this on board.

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Australia's TGA Overrides Industry Concerns Over Publishing Priority-Review Pathway Decisions

NEENA BRIZMOHUN neena.brizmohun@informa.com

Australia's Therapeutic Goods Administration will be publishing the decisions it makes on medical devices and IVDs eligible for designation under its forthcoming priority-review pathway for expediting access to novel products, despite industry's concern that doing so would introduce a competitive disadvantage for manufacturers.

Publishing these decisions will provide useful information and clarity for consumers, industry and health professionals, the TGA said of the change it has made to the priority-review pathway after considering feedback from a public consultation on a proposed version of the initiative.

Industry does not necessarily agree. Publishing applications is not relevant to the assessment phase of the process, biotechnology industry group AusBiotech said in its newly published submission to the consultation. Current application decisions are not published and priority-review applications should not be treated differently, according to the trade group.

Publishing these decisions would introduce "a disclosure that could disadvantage the device owner with no accompanying benefit for the public, therefore imposing a competitive disadvantage," the industry group argued. The move also "appears to be against the intent of the Advertising Code that prohibits the mentioning of unapproved devices, so as to not create unrealistic expectations on device availability."

BROAD SUPPORT, BUT MODIFICATIONS REQUESTED

AusBiotech's comments were published on TGA's website on June 19 along with submissions from other stakeholders who responded to the consultation, which ran from Nov. 16, 2016, to Jan. 11, 2017. The priority-review pathway is designed for breakthrough products for serious unmet needs. It will allow applications for conformity assessment or inclusion on the Australian Register of Therapeutic Goods to jump to the front of the queue.

The consultation submissions "showed broad stakeholder support for the proposed approach," TGA commented, adding that modifications were proposed, particularly in relation to timeframes and publication for designation decisions. "Stakeholder feedback has informed the policy position going forward and the upcoming changes to the Therapeutic Goods Regulations 1990," said the agency, which has published a summary of policy changes resulting from the feedback in an outcome summary.

For example, TGA has decided to shorten the time it will take to review the applications it receives for priority review designation from six weeks to a maximum of four weeks.

The original six-week review proposal was, according to Johnson & Johnson, "too lengthy and may reduce any real gain in overall review times given the device will still be required to undergo standard assessment processes."

Also, designation decisions will lapse after six months instead of three months, as proposed in the consultation, according to the outcome summary.

TGA also decided to go ahead with a proposal that IVD-makers object to – the introduction of an additional criterion for IVD applicants to show that the early availability of their product in Australia will result in a major public health benefit.

Industry association IVD Australia does not agree that priority should be only based on public-health benefit. "Early availability in Australia could result in a major public OR personal health benefit. For example, a prenatal test to definitively rule out genetic predisposition to a condition leading to serious deterioration in quality of life at an early age could be deemed a critical clinical need," the trade group wrote.

CONCERNS OVER QUEUE-JUMPING

IVD Australia also had concerns over the new pathway's queue-jumping system. "Devices designated for Priority Review, which go to the front of the queue, should not be placed ahead of submissions that are, say, 90% complete," the group said. "Submissions at this stage of assessment, which have gone through the 'Business as Usual' pathway, will most likely have been under assessment for a lengthy period of time as it is. To further penalize these applications is unacceptable and would potentially lead the TGA to go beyond allowable timeframes, where these apply; for example, 255 working days for design examination. Also, as TGA themselves have stated, to pick up a submission after a lengthy break causes longer review times, as the assessor must get back up-to-speed on the submission. "

The Medical Technology Association of Australia urged TGA to resource the priority review pathway adequately so routine applications are not delayed.

The plan to introduce the priority-review pathway follows the government's September 2016 response to the Medicine and Medical Devices Regulation (MMDR) review on how to reform and enhance the regulatory framework for health-care products.

TGA said it was currently considering all submissions that were received as part of the priority review pathway consultation. "Further information on process details of the Priority Review pathway that has been informed by this consultation will be included in guidance documentation, to be released on the TGA website closer to the pathway's implementation date" of Jan. 1, 2018, it said.

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Christopher Keeling
+44 203 377 3183
christopher.keeling@informa.com
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