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Pain Management I: Spinal Cord Stim To Grab Ever-Bigger Market Share

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New advances in spinal cord stimulation (SCS) systems, including those that offer different waveforms and frequencies and better address different populations, have elicited excitement in the medical community. This is especially the case in the US where the opioid epidemic has led to increased scrutiny of doctors' prescription habits and alternative non-drug options for managing pain. Some US legislators and the new US FDA Commissioner, Scott Gottlieb, are also advocating for the use of devices at least as a partial solution to the nation's opioid crisis. *(Also see "Gottlieb Touts Devices For Pain Control To Help Solve Opioid Crisis" - Medtech Insight, 6 Apr, 2017.)*

This article, the first of a two-part series focusing on pain management, will delve into the promise of using SCS systems from the physicians' point of view, analyze the global SCS systems market and identify what's driving, and impeding, the wider adoption of these technologies.

SCS: PROMISING ANSWER FOR MANY CHRONIC PAIN ETIOLOGIES

According to a new report by *Meddevicetracker*, "Pain Management Devices Market," worldwide sales of SCS systems are expected to climb from $1.8bn in 2016 to $2.4bn in 2021, a CAGR of 6%. This represents a market share for SCS of 55.2% in 2016, which it is expected to retain the lion's share of by 2021.

SCS systems are increasingly being used by anesthesiologists, orthopedic surgeons and physiatrists to address difficult-to-manage pain patients. While there is already high-level proof for the safety, efficacy and cost-effectiveness (Level I-II) of traditional SCS therapies in treating chronic refractory low back pain with predominant limb pain, the more sophisticated next-generation SCS systems promise an even more targeted approach and wider applicability.

Traditional SCS therapy uses a small battery-powered pulse generator that transmits low-voltage electrical stimulation to spinal nerves to block the feeling of pain, substituting it with paresthesia. In recent years, device-makers -- including such giants as **Medtronic PLC**, **Boston Scientific Corp.**, **St. Jude Medical Inc.** (now **Abbott Laboratories Inc.)** and smaller players like **Nevro Corp.** -- have introduced next-generation technologies with novel stimulation parameters including burst SCS, dorsal root ganglion SCS and high-frequency SCS that have shown compelling results in clinical trials. These new therapies, which are much more tar-

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Medtech insight

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EUROPCR 2017:

Boston Scientific's Lotus TAVR Beats Medtronic's CoreValve In REPRISE III, But Pacemaker Issue Remains

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REPRISE III, the largest randomized, head-to-head comparison of two transcatheter valves, has reassured **Boston Scientific Corp.** that its *Lotus* repositionable, mechanically expanded transcatheter aortic valve will be able to compete with the more established TAVR systems once it reaches the market.

Ted E. Feldman of the NorthShore University HealthSystem in Evanston, Illinois presented one-year results from the global, multicenter trial at the the EuroPCR Scientific Program in Paris on May 16. REPRISE III randomized 912 patients severe aortic stenosis and extreme or high operative risk to transcatheter valve replacement with Lotus or **Medtronic PLC**'s *CoreValve* system on a 2:1 ratio.

Lotus beat CoreValve for the primary effectiveness endpoint, a composite of the rate of all-cause death, disabling stroke, and at least moderate paravalvular aortic leakage at one year – 16.7% versus 29.0%. Lotus patients had a significantly lower combined rate of all-cause mortality plus disabling stroke – 13.2% versus 17.9%, and a significantly lower rate of disabling stroke – 3.6% versus 7.3%. However, the study was not powered for superiority on this endpoint and Feldman told *Medtech Insight*,"Statistically this was better for Lotus than CoreValve, but the CoreValve stroke rate was unexpectedly high and I don't think it represents the typical high-risk patient population that we see."

Boston Scientific expects to reintroduce Lotus into Europe later this year taking it off the shelves in response to manufacturing flaws. It is counting on REPRISE III to support US FDA approval of Lotus by late 2017. *(Also see "OUS Approvals Analysis: BSX, Edwards Score New CE Marks In TAVR Battlefield; Chinese DES Advances In Asia" - Medtech Insight, 10 Oct, 2016.)*

The encouraging news about Lotus comes the same day that Boston Scientific closed its acquisition of **Symetis SA**, a smaller European TAVR company marketing the *Acurate neo TF* TAVR system and the *Acurate TA* system designed specifically for the transapical approach. Some observers suspected Boston Scientific's acquisition of another TAVR company indicated that it is losing confidence in Lotus, especially after it had to pause all implants of Lotus in February to address a manufacturing problem with the delivery system. *(Also see "Symetis TAVR Buy Not About Throwing Shade On Lotus, BSX Insists" - Medtech Insight, 30 Mar, 2017.)*

During a May 16 conference call to discuss the REPRISE III results, Kevin Ballinger, the president of Boston Scientific's Interventional Cardiology business, said, "Boston Scientific has the most compelling and differentiated TAVR portfolio now in the industry with the addition of the Symetis Acurate valve and the Lotus platform. And I couldn't be more excited about the prospects for us in that space, so I feel that's one of the largest, fastest-growing markets in interventional cardiology." Both Lotus and Acurate are available in Europe, but neither is approved by US FDA. Boston Scientific believes the worldwide TAVR market will be worth $4bn market by 2020.

Boston Scientific's *Lotus* Transcatheter Aortic Valve

Source: Boston Scientific, Inc.

"What this portfolio really offers is physician choice and really the best treatment for each patient anatomies, and that comes from one company. To have that portfolio under one company's umbrella, I think can be quite powerful," Ballinger said. "The strong REPRISE III data, I think was very reassuring. Lotus is known for best-in-class paravalvular leak rates, which is very important; and also the ability to fully assess the valve's performance upon deployment. So, that's reassuring for physicians as well."

LOTUS BEATS COREVALVE FOR STROKE AND LEAK RATES

In addition to beating CoreValve in the primary efficacy endpoint in REPRISE III, patients treated with Lotus in the trial also had significantly lower rates of moderate-to-severe paravalvular leak compared to the CoreValve patients – 2.0% vs. 11.1% – and the Lotus patients were also significantly less likely than the CoreValve patients to need a repeat procedure to repair problems with the first valve implant, or to suffer a valve malapposition.

Lotus was statistically non-inferior to CoreValve for the primary safety endpoint, a composite of all-cause mortality, stroke, life-threatening and major bleeding events, stage two or three acute kidney injury, or major vascular complications through 30-days post-implant.

However, the Lotus patients had a higher rate of valve thrombosis than the CoreValve patients at one year – 1.5% versus 0% – and the Lotus patients were more likely to need a pacemaker – 35.5% versus 19.6%, a problem that has plagued Lotus since its earliest human trials. The company has tried to address the pacemaker issue by adding a *Depth Guard* to the next-generation *Lotus Edge*.

The higher pacemaker rate compared to CoreValve "is something we've seen with this first-generation Lotus device, but other reports have shown that there's a learning curve, and that even with this first-generation device, pacemaker device get better with experience," Feldman said. Boston Scientific has redesigned the deployment mechanism for Lotus so the next-generation Lotus Edge has a "top-down" rather than "bottom-up" mechanism that requires less interaction between the valve and the left-ventricular outflow tract, thereby reducing the chances that the TAVR procedure will interfere with the atrioventricular node. Feldman said that preliminary data from the RESPOND EDGE registry shows the pacemaker rates with the second-generation valve at hospital discharge are 20%.

Feldman credits the Lotus' performance in REPRISE III to the fact that the valve can be visualized, assessed, and then repositioned during the implant procedure to ensure ideal positioning. He credited Lotus' *Adaptive Seal* polycarbonate-based urethane seal for the low rates of paravalvular leak seen in the Lotus patients in REPRISE III.

"The takeaway [from these results] is that Lotus performed well and that any concerns that people have expressed about repositioning being an increased stroke risk are not born out by this endpoint. The real driver for the effectiveness-superiority was paravalvular leak, which was much lower for Lotus than CoreValve," Feldman told *Medtech Insight*. "The ability to accurately position the valve and adjust the position to eliminate paravalvular leak is the unique finding in the trial and this was further reflected by the absence of malpositioning or need for a second valve in the Lotus group, whereas several valves in the CoreValve group had to have a valve-in-valve procedure to treat malposition on the first implant."

Lotus boasts a mechanical expansion system that is distinct from either the balloon-expansion technology in **Edwards Lifesciences Corp.** *Sapien* line of TAVR devices or the self-expansion technology in Medtronic's CoreValve systems. "It's a different and completely unique design and deployment mechanism. It's neither self-expanding nor balloon-expandable, it's a controlled mechanical expansion. It's clearly an advance in terms of paravalvular leak and malpositioning," Feldman said.

ANALYSTS: REPRISE III IS "SURPRISING" AND "REASSURING"

In a May 16 note on the REPRISE III presentation at EuroPCR, Wells Fargo analyst Larry Biegelsen writes that the results were "reassuring" after the recent Lotus recall, the Symetis acquisition, and fears among some observers that Lotus would yield more strokes than CoreValve.

"The pacemaker rate with Lotus is still too high according to most physicians but Boston Scientific expects the pacer rate to be competitive with its new Lotus Edge design," Biegelsen notes. However, he said, "it's worth noting that docs we've spoken with recently are skeptical Boston Scientific will be able to reduce the pacer rate with Lotus Edge." At the same time, Boston Scientific the Symetis *Acurate Neo* has a relatively low pacer rate, "which makes it complementary to Lotus," Biegelsen states. "The REPRISE III data should help Lotus recapture share it lost due to the recall, but Medtronic will be able to counter the data to avoid significant share loss."

He points out that REPRISE III used an older version of Medtronic's CoreValve valve, and that the newer *CoreValve Evolut Pro,* recently launched in the US, has a skirt which reduces the paravalvular leak rate. *(Also see "ACC 2017: SURTAVI Supports Intermediate-Risk Intervention For Medtronic's CoreValve" - Medtech Insight, 21 Mar, 2017.)*

On the same day, Jefferies analyst Raj Denhoy wrote, "The superiority on paravalular leak was expected, but the win in stroke was not. The study was not powered for superiority and even the presenters noted that the higher stroke rate for CoreValve was likely due to chance." Regardless, he said, "With positive headlines for Lotus and Symetis closing, Boston Scientific is off to a strong start at PCR."

Boston Scientific's Lotus and Acurate valves are "an intriguing combo and offer solutions for a wide range of pathologies (heavy calcification, anatomic anomalies, etc.)," Denhoy concludes. "The combo de-risks Boston Scientific's place in the market—should either valve stumble."

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Consumer-'Empowering' Devices Called Out In Gottlieb's First FDA Speech

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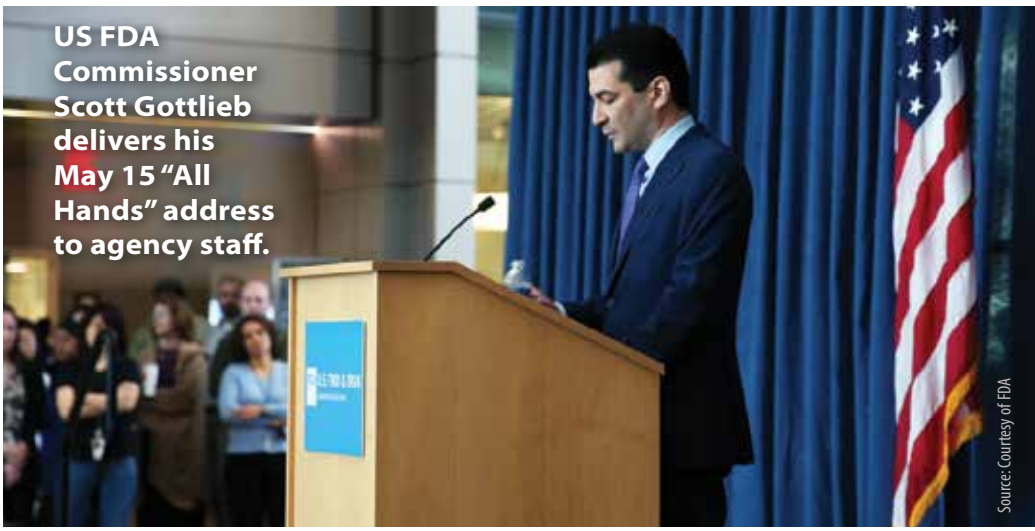
Scott Gottlieb's first speech as commissioner to US FDA staff included only one direct mention of medical devices, referencing realms of technology that Gottlieb has previously urged the agency to stay out of as much as possible: direct-to-consumer genetic testing and digital health.

Gottlieb, who was sworn in as FDA commissioner May 11, delivered his first address to the agency during an "All Hands" meeting on May 15; the text of the speech was posted on FDA's website.

In pointing to "new scientific opportunities" that make him optimistic for the future, he cited gene therapy, regenerative medicine, and "new medical devices that are empowering consumers, enabling them to be better informed about their health, and better stewards of their own medical care."

This description most directly references DTC genetic testing services and digital-health tools, two categories of product that have been the subject of significant debate in recent years over FDA's proper regularly role. These are debates that Gottlieb has actively engaged in during his time outside of government as a think-tanker and commentator, arguing for FDA to back off, and let innovators innovate and patients gain unfettered access to their own health data. And less oversight in these areas is largely the direction that the agency, and congressional reforms to the agency, have taken in recent years, potentially contributing to Gottlieb's optimism.

The DTC testing issue has played out most publicly in FDA's interactions with **23andMe Inc.** Gottlieb, then a resident fellow at the American Enterprise Institute, severely criticized the agency's 2013 letter calling on 23andMe to stop selling its DTC carrier-screening and risk-predisposition genetic testing service without submitting data to FDA. *(Also see "FDA Comes Down Hard On 23andMe, Putting Consumer-Directed Genetic Testing On Notice" - Medtech Insight, 25 Nov, 2013.)* Gottlieb argued



US FDA Commissioner Scott Gottlieb delivers his May 15 "All Hands" address to agency staff.

Source: Courtesy of FDA

FDA didn't have the authority to regulate people's access to information linking their own genetic code to estimated risks based on scientific studies. In a 2013 editorial in the publication *Real Clear Markets*, Gottlieb said FDA's letter was "unscientific" and "may also be unconstitutional."

Since then, FDA has engaged in an apparently collaborative process with 23andMe, leading to *de novo* classifications and market access for certain carrier-screening and risk-predisposition testing services, and establishing a pathway that will not require additional pre-market review for future test offerings from the firm and might speed the path for other DTC genetic test firms, as well. *(Also see "23andMe Opens Up FDA Pathway For DTC Genetic Predisposition Tests" - Medtech Insight, 6 Apr, 2017.)*

Gottlieb, who has served on the HHS Office of the National Coordinator for Health IT Policy Committee, has similarly pushed for a hands-off approach by FDA to mobile apps and clinical decision support software, which he puts in the same category as consumer gene tests – all tools linking a patient's health information with published data.

FDA has, by-and-large, moved in this direction in recent years via guidance documents and other policies that have exempted an array of app and software categories from active oversight. And, late last year, the 21st Century Cures Act was enacted with provisions that remove five categories of health software, including clinical decision support, from FDA's authority. *(Also see "'Cures' Bill Circumvents FDA On Medical Software Regs" - Medtech Insight, 30 Nov, 2016.)*

With the evolution toward a reduced FDA footprint on consumer genetics and digital health, it remains to be seen whether Gottlieb will press for an even lighter touch or simply plans to keep policies on their current course.

'CURES,' OPIOID PRIORITIES

The new commissioner made no mention of any other device-specific issues during his speech. He did say that implementing the Cures Act will be a "key priority," noting that "Congress gave us a clear mandate to be forward-leaning when it comes to how we'll evaluate safety and efficacy in view of emerging scientific insight and better analytical tools." In addition to the software provisions, the Cures Act includes a Breakthrough Devices pathway, strengthens the agency's emphasis on "least burdensome" approaches to device

oversight, and simplifies FDA's process recognizing new consensus standards, among other streamlining reforms. *(Also see "21st Century Cures: Device Provisions" - Medtech Insight, 14 Dec, 2016.)*

Gottlieb discussed specific policy priorities in the realm of drug pricing, food safety and tobacco oversight. But, he said, "unquestionably, our greatest immediate challenge is the problem of opioid abuse." Although he did not address devices in this context during the speech, Gottlieb highlighted the role devices, such as novel pain pumps, could play in countering opioid addition by serving as pain-treatment alternatives. *(Also see "Gottlieb Touts Devices For Pain Control To Help Solve Opioid Crisis" - Medtech Insight, 6 Apr, 2017.)*

"I'll be working with FDA's senior career leadership, and in the coming weeks hope to have more to say on how we take even more forceful steps to address this crisis," Gottlieb said May 15.

One issue that received no mention during the speech is the reauthorization of FDA user fees for devices, drugs, generics and biosimilars. Device industry groups have said that their top near-term priority for Gottlieb is his support for quick passage of industry-FDA user fee agreements – which include enhanced pre-market review performance goals and new programs and investments from FDA in return for increased user fees. *(Also see "With Gottlieb Sworn In, His Focus Should Be On Quick User-Fee Passage, Industry Advocates Say" - Medtech Insight, 11 May, 2017.)*

Gottlieb also did not directly address another issue that was left unresolved at the end of the Obama administration – FDA's policy on overseeing off-label, but truthful product communications by product sponsors. *(Also see "Unapproved Indications Guidance Proves Controversial" - Medtech Insight, 26 Apr, 2017.)*

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Robert Califf Talks Verily, Hopes Gottlieb Can Push Back On Trump

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Former US FDA Commissioner Robert Califf confirmed May 17 that he is joining digital health and medical device company Verily Life Sciences as an advisor. In an interview with *Medtech Insight*, he spoke about the new position, and also discussed the new FDA Commissioner Scott Gottlieb. Califf says Gottlieb was clearly the most qualified candidate, but hopes he will be ready to push back against any unreasonable demands from President Trump.

Listen to the entire interview via the podcast player below:

Califf's new job with Verily will allow him to maintain his professorship at Duke University while also joining Stanford University as an adjunct professor. He says he hopes to use the new position to help bridge the gap between technology and health-care services.

The news that Califf would be joining the company formerly known as Google Life Sciences was first reported by CNBC on May 16. The former FDA commissioner confirmed it in a blogpost on Verily's website.

"Although we are in the midst of an explosion of capability in the worlds of computing and information, we are still learning how to translate this capacity into better health and health care," writes Califf. "Bridging this gap has been a recurring theme of my career, and it's at the heart of what I hope to accomplish" at Verily and Duke.

Robert Califf

LISTEN

To hear the full interview with Robert Califf, go online to http://bit.ly/2qRVgzK.

In an interview with *Medtech Insight*, Califf says he'll be able to bring a strong regulatory background to the company.

"The amount of information that you ingest as FDA commissioner and the expert way in which you get briefings that inform you about entire areas of science and industry are just phenomenal. I'm hoping – Verily is involved in a lot of different things – as I help out, I'm expecting that things that I learned along the way will be very helpful."

Verily is engaged in a broad range of projects and partnerships with device, drug and technology firms, including miniaturized continuous glucose monitors, surgical robotics, population health tools and precision medicine databases.

Califf is very optimistic about the progress made in the 21st Century Cures legislation and the user fee reauthorization bills that are moving through Congress for approval now. He says the medical products industries should pay particularly close attention to review-process changes at FDA, as well as ORA's "program alignment" facility inspection initiative. *(Also see "US FDA's 'Program Alignment' Inspection Scheme Begins" - Medtech Insight, 15 May, 2017.)*

and *(Also see "'Program Alignment' Falls Into Place: Everything You Need To Know About US FDA's New Inspectional Approach" - Medtech Insight, 8 May, 2017.)*

ORA is FDA's Office of Regulatory Affairs, which conducts all of the agency's field activities.

While he already misses his colleagues at FDA, Califf says he's confident in Gottlieb.

"Scott is clearly the best candidate of the pool of candidates; he's well prepared," said Califf. "He's worked with the FDA before, he's a doc, so he understands the medical products side quite well; people like him at the FDA who worked with him before, and his experience the last few years in product selection – at GSK for example – has given him … a lot of insight into the issues that come up in technology development, and I think that will be important.

If the president makes any unreasonable demands of FDA, Califf says he hopes the new commissioner will take a stand.

"I hope that he'll be able to stand up if there are any whimsical directives from the president, which [could be] a tweet in the middle of the night, or something like that. Who knows what might happen there," he said. "If that happens, he'll need to be strong."

In the interview, Califf also talked about the digital health industry in general, stating that while he expects a majority of digital health companies to fail, he is also confident that a significant number of them will bring products to market that will change the health-care landscape.

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NEST Executive Director: A One-Woman Army

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After years of debate and discussion, the public-private National Evaluation System for health Technology (NEST), which FDA officials have said will re-make device data collection in the US, is finally getting off the ground. Leading the endeavor is Rachael Fleurence, who took on the role of executive director of NEST's Coordinating Center last month.

Over the next year, Fleurence will work with stakeholders to develop a NEST five-year plan and begin hiring staff to help build the system that can leverage real-world evidence from registries and other electronic sources, apply advanced analytics, and pool knowledge and resources to enhance the data that is available to support pre-market and post-market decisions for devices. She spoke to *Medtech Insight* about her plans. Listen to the interview in the podcast player below:

Fleurence's first day at the NEST Coordinating Center was April 24, and so far she's the only full-time employee. Other than assistance from the Medical Device Innovation Consortium (MDIC), which has been instrumental in the project's creation, Fleurence is working with consultants to get NEST off the ground. *(Also see "A New NEST: MDIC Leaders Discuss Relocation, National Evaluation System And More" - Medtech Insight, 27 Apr, 2017.)*

"The team will likely grow, I'd say between two and 10 full-time employees within the next year," she told *Medtech Insight*.


Rachael Fleurence

LISTEN

To hear the full interview with Rachael Fleurence, go online to http://bit.ly/2rPeYeu.

A veteran of the Patient-Centered Outcomes Research Institute (PCORI), Fleurence headed its National Patient-Centered Clinical Research Network, or PCORnet, for the past five years. She says that experience has helped her understand the opportunities and challenges of running a large clinical research database.

"Having spent five years doing that work on the comparative-effectiveness research side, I'm going to be bringing a lot of that experience...to the work at NEST," said Fleurence.

NEST has been a labor of love for FDA and especially CDRH Director Jeff Shuren who has long touted its potential to industry. It responds to inherent hurdles in collecting device data via controlled trials, and a lack of connected, public real-world databases available for devices to support critical decision-making. *(Also see "Shuren At FDLI: Least-Burdensome, Real-World Evidence Efforts Picking Up" - Medtech Insight, 10 May, 2017.)*

FDA says NEST can help not only follow medical devices long after they are introduced into the market to gather real-world evidence to look for safety signals, but also allow some devices to get to patients sooner with less pre-market data requirements that are contingent on more post-market data.

"It's really time for a paradigm shift to move from our [current] system to a system that supports better, faster, cheaper evidence generation for medical devices," said Fleurence. "Part of the excitement is that there is leadership in the medical device industry and the FDA to really work together to transform this ecosystem for the benefits of patients."

Industry has cautiously signed out the

effort, agreeing to provide some funding via the upcoming MDUFA IV user fee program to support pilot the NEST program, but it took some convincing. *(Also see "Industry, US FDA Strike $1Bn Deal After Contentious User-Fee Negotiations" - Medtech Insight, 23 Aug, 2016.)*

As NEST takes off, the first order of business for the project will be to establish a governing committee this summer that includes stakeholders representing patients, clinicians, the device industry, payers and FDA. That committee will immediately work on developing a five-year strategic and operational plan for NEST.

Other milestones NEST aims to complete by the end of the year, according to Fleurence, include identifying demonstration projects and a sustainability plan that ensures NEST can continue to operate beyond its five-year pilot funding. She says the key will be making sure the project shows value to all stakeholders including the medical device industry, patients and payers.

As for the first products that are likely to take advantage of NEST, Fleurence says so far evidence suggests cardiovascular and orthopedic devices are likely the best positioned to benefit. *(Also see "Pilot Of New US Evaluation System Will Include At Least Two Devices" - Medtech Insight, 31 Oct, 2016.)*

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Panel Recommends Approval Of Lung Transplant Device, Despite FDA Concerns

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Serious US FDA concerns about clinical trial conduct didn't get in the way of a favorable panel recommendation for the *TransMedics Organ Care System* (OCS) from **TransMedics Inc.**

The portable device helps preserve donor lungs for transplant by ventilating, perfusing and monitoring them, effectively making the lungs breathe during transit. The 13-member gastroenterology and urology devices panel voted to recommend approval of the device on May 17, with a vote count of 11-2 in favor of safety; 8-5 that it was effective; and 9-4 that the benefits of the device outweighed the risks.

But during the course of the daylong meeting, FDA staff and panelists alike repeatedly voiced concerns about TransMedics' INSPIRE pivotal trial. The trial, which ultimately enrolled 349 patients, underwent significant changes to its study design and analysis plan throughout the course of the study. Specifically, the original primary endpoint was to be a composite measure of patient survival 30 days after transplant and the absence of a specific adverse event at 72 hours after surgery. But TransMedics altered the endpoint to include adverse events that occurred within 72 hours.

The problem, FDA lead device reviewer Andrew Fu said, was that the manufacturer had access to unblended outcome data from 227 of the 329 patients before the endpoint was changed, opening the possibility that it had been changed based on knowledge of the trial results.

In addition, the sponsor changed the trial population after 71% of the transplants had been performed by eliminating any patients who were subject to major protocol violations. The protocol violations included device malfunction, as well as opening a randomization envelope out of order. In addition, 41 sets of lungs came from donors who should have been screened out for a variety of reasons. FDA had advised against the change to the trial population.

Company CEO Waleed Hassanein took responsibility for the failures, but still offered a strong defense of the trial results.

"The patient death at 30 days occurred at the site with the highest rate of protocol violations, and the patient never met the eligibility criteria," he said. "The deaths were strokes and allergic reactions to drugs. There hasn't been a single death related to device malfunction."

His comments drew a sharp rebuke from FDA review division director Benjamin Fisher. "None of that information was provided to FDA, and it's borderline inappropriate not to include it in the PMA," he said. "This is not to be a summation of your research. It's meant to be a panel discussion."

FDA also said that some trial results weren't much better than the standard of care. About 79% of the final trial population met the final endpoint, compared to 71% of the control population. This is below the non-inferiority margin. In addition, OCS patients experienced higher 30-day mortality.

"If someone showed this data to a patient and asked them to choose this or the standard of care, they'd probably choose standard of care," said consumer representative Naftali Frankel.

However, TransMedics and some stakeholders argued that OCS could significantly improve prospects for patients who need lung transplants. Currently, 15% of patients on a waiting list die before they get new lungs, and only 20% of donor lungs are retrieved. And conventional preservation techniques have been tied to certain kinds of lung injury. The company also said the higher mortality wasn't related to the lung transplants themselves.

Gabriel Loor, a lung transplant surgeon at Baylor College of Medicine and TransMedics trial leader, said that the device could represent the first advance in organ preservation in 30 years.

Despite the ultimate recommendation, the panel ended with a note of caution.

"The sponsor said they'd never do a trial like this again, and they should take those comments to heart," said panel chairman Steven Schwaitzberg. "This could have gone either way. The votes were a near thing."

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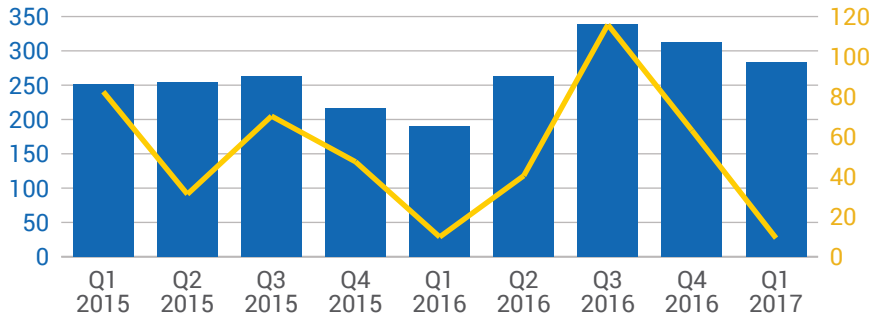
SNAPSHOT: Device Recalls Q1 2017

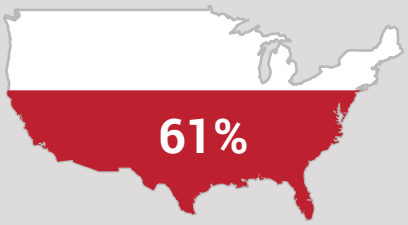
There was a slight decrease in the number of medical device recalls in Q1 2017. There were 284 recall events from January through March, down 9% from Q4 2016's 313 corrections and removals. But that's still higher than seven of the past 10 quarters, according to consulting firm Stericycle, which gathered its recalls data from FDA Enforcement Reports. The number of recalled device units saw a massive 85% decrease, falling to 9,281,706 units in Q1 2017, from 63,102,245 in Q4 2016. That's the smallest number of recalled units since Q4 2013, Stericycle says.

MEDICAL DEVICE RECALLS & UNITS (in millions)



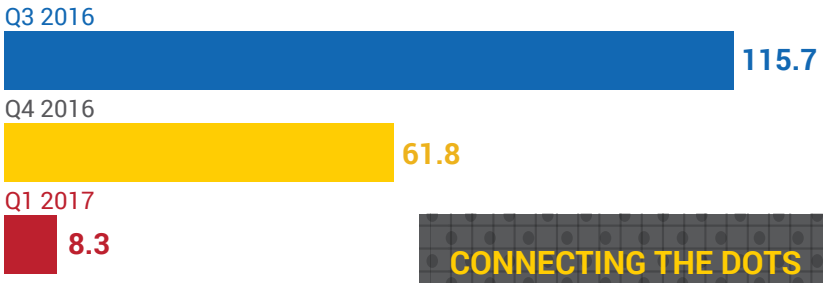
DEVICE DANGERS

10% of recalled units were high-risk class I, the highest percentage since Q3 2014.



OF DEVICE RECALLS WERE NATIONWIDE

CLASS II UNITS RECALLED BY QUARTER (in millions)



TOP RECALL CAUSES BASED ON UNITS

Sterility Issue	Software Issue	Quality Issue	Mislabeling Issue
29.2%	24.4%	22%	10.6%

CONNECTING THE DOTS

- The average recall size was 32,682 units, the lowest average recalls size for a quarter since Q4 2013.
- 54.2% of recalls were for software or mislabeling — the same top two reasons as Q4 2016.
- 44% of recalls were distributed both domestically and internationally, the lowest percentage in four years.

Source: Stericycle ExpertSOLUTIONS Q1 2017 Recall Index

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45% Leap In Notified-Body Certificates Withdrawn From Device Firms

Bankruptcy, invoices not paid, and inability to close major non-conformities were among the many reasons that EU notified-body certificates were withdrawn from device companies in 2016, according to survey results from the TEAM-NB EU notified body association. But the 45% increase in TEAM-NB certificate withdrawals last year, in addition to a consistent decline in the number of certificates issued, likely reflects the increasingly challenging EU regulatory environment faced by medtech, TEAM-NB suggests.

In total, 1,881 certificates were withdrawn from device firms by TEAM-NB members last year, up from 1,294 withdrawals in 2015, according to data reported in the association's Medical Device Survey 2016, based on figures presented by 21 member notified bodies. (TEAM-NB has subsequently gained one additional member.) The total represents an average of 90 withdrawals per notified body last year.

In some instances, the withdrawals resulted from a device company's inability close major non-conformities. In other cases, it stemmed from financial issues. Decisions by firms to transfer to another, sometimes cheaper, notified body also factored in the data.

According to TEAM-NB, the large overall increase may reflect increasing EU regulatory expectations and notified bodies tightening up their standards on companies as a result. Indeed, the European Commission's plan of actions, including the joint audits by designating authorities of notified bodies, have made the environment much tougher, even in advance of the new Medical Device and IVD Regulations.

The number of certificates withdrawn has been steadily increasing since 2013, but the spike in 2016 accelerates the trend. The 2016 rise was double the 22.3% increase in 2015.

TABLE 1

TEAM-NB Certificate Withdrawals

YEAR	NUMBER OF CERTIFICATES WITHDRAWN BY TEAM-NB NOTIFIED BODIES
2016	1,881
2015	1,294
2014	1,058
2013	881

Meanwhile, the number of new certificates issued to device firms has steadily dropped since 2013, to a low of 4,098 new certificates in 2016. TEAM-NB speculates that the increase in requirements, and in the time it now takes to obtain certification, along with the number of current applications that don't result in a certificate, is most likely affecting the number of certificates issues.

TABLE 2

Team-NB Certificates Issued

YEAR	NUMBER OF NEW CERTIFICATES ISSUED BY TEAM-NB MEMBER NOTIFIED BODIES
2016	4,098
2015	4,480
2014	4,535
2013	5,061

Other interesting certificate-related data from the TEAM-NB survey:

- The aggregate total of valid certificates issued as of 2016 also dropped – from 21,037 in 2015 to 19,753 in 2016. This averaged out to 941 per notified body in 2016, compared with 956 per organization in 2015;
- Six of the 21 notified bodies issued more than 1,000 certificates in 2016, while five issued between 350 and 1,000, and 10 issued less than 350; and
- In total, 91% of certificates were issued under the Medical Devices Directive, just 7% under the IVD Directive, and 2% under the Active Implantable Medical Devices Directive.

STAFFING GROWS, BUT IS IT ENOUGH?

As certificate numbers are dropping, notified bodies are steadily growing in terms of staff size. There was a 12% increase in the number of full-time employees working with TEAM-NB members in 2016. This is the fourth year in a row that there has been an overall increase.

But, interestingly, this staffing growth comes as the overall number of EU notified body organizations are declining. The number of TEAM-NB notified body members dropped from 28 to 21 between 2013 and 2016. And the number of EU notified bodies overall, regardless of membership, has fallen from almost 80 several years ago, to 54, including a recent drop-out that occurring in only the past few days. *(Also see "More EU Notified Bodies Bite The Dust" - Medtech Insight, 17 May, 2017.)*

During the three years that the number of TEAM-NB members have dropped, full-time employees grew by 87%. The increase in full-time-equivalent hiring reflects the need by notified bodies to meet new demands and anticipate the additional workload that will be demanded by the new EU requirements. But Françoise Schlemmer, director at TEAM-NB, said that the most recent 12%

TABLE 3

Notified Body Staffing

Average number of full-time equivalents working in the medical devices sector

YEAR	FULL-TIME EQUIVALENT EMPLOYEES	FULL-TIME EQUIVALENT CONTRACTORS
2016	86	25
2015	77	28
2014	65	25
2013	46	26

workforce increase has probably not yet trickled down into actual improvements in notified body capacity. It takes a year to train a new auditor, she pointed out.

Device companies and others are questioning whether notified bodies will have the capacity available that is needed to address upcoming responsibilities under the Medical Device and IVD Regulations. The new regulations enter into the force of law on May 25, and will fully apply in 2020 and 2022, respectively.

While there is a long transition period for companies to achieve compliance with the new regulations, all products – both new devices and those currently on the market – will ultimately need to be reviewed under the new rules. This means that a massive number of audits will need to be carried out in a limited amount of time.

Resources will be particularly tight for IVD products, because some 85%-90% of IVDs will need to be reviewed by notified bodies under the new regulations, up from only about 10%-15% that require such oversight under current requirements.

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Time Running Out For Compliance With Ukraine Device Law

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Ukraine has long been shadowing EU legislation and regulation via its draft Agreement on Conformity Assessment and Acceptance (ACAA) of industrial products. The country has already developed technical regulations that are almost fully aligned with the respective EU directives in some sectors.

In early 2017, the EU and Ukraine consolidated their relationship with a Deep and Comprehensive Free Trade Area (DCFTA), which will take seven years to come into effect in full.

The local medical device sector is impatient, however, for closer alignment with EU regulation. And Maxim Bagreev, CEO of Kiev, Ukraine-based Cratia, a medical product regulatory consultancy, says device harmonization has not been a top priority nationally.

Nevertheless, Ukraine now stands on the threshold of a key date toward an EU harmonized. *(Also see "Ukraine Conformity Assessment System On Track But Challenges Lie Ahead" - Medtech Insight, 6 Apr, 2016.)*

On July 1, the country is slated to officially transition from the old, state-based medical device regulation to the new, decentralized EU-style system, based on Declaration of Conformity (DoC). The deadline has been extended already. *(Also see "Ukraine Medical Device Industry Gets Hoped-For Transition" - Medtech Insight, 22 Apr, 2016.)* But manufacturers should not count on a repeat of that, Bagreev suggests. For overseas manufacturers, this also means the end of the import of medical devices under the old registration certificates.

But products still in circulation with valid registration certificates before July 1 may remain on the market for five years, or until the expiry date of the medical device, whichever comes sooner. No further action is necessary to keep these products on the market in Ukraine.

Only new certificates will be issued after July 1, which is less than two months away. "It will be a big test for the market in general,

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and manufacturers and authorized representative (ARs) in particular," says Bagreev. He adds that in the past two years, companies and ARs have had to perform new procedures, apply to notified bodies, and get audits done. Cratia has played its part in this process, auditing some 250-300 companies – some 25% of companies serving the Ukraine market, including some of the global majors.

REGISTRY PROGRESS

Another element in Ukraine's new medical device regulatory structure – a national registry of entities responsible for introducing medical devices, implantables and IVDs onto the market – was established earlier this year with the passage of Ministry of Health Order No. 122. The order, passed into law on April 18, establishes procedures for keeping the registry, the data required and how they are accessed.

The scope of the order, aimed at manufacturers and ARs, includes all class I medical devices (including sterile, and those with measuring functions), custom-made devices, systems and procedural packs; all IVDs; and custom-made active implantable medical devices. Bagreev notes that information on class II and III devices will enter the registry via notified bodies, which will submit the information to the competent authority.

Bagreev points out that there are still many questions and problems concerning the registry. The Technical Regulations that form the basis of the new Ukraine device regulatory system (Nos. 753,754 and 755) were published in 2013. *(Also see "Ukraine's new medtech regulations in force, transition decision awaited" - Medtech Insight, 8 Jul, 2015.)* They each make reference to the registry, "but we've had several years without a registry and some parts of [it] are still under development," Bagreev complains.

The company is pressing for answers to questions on the need to re-submit information where data have already been submitted in the past. It also wants to know whether information should be submitted for all IVDs –including those in List A and B of the Annex 2 of Technical Regulation 754 – as the same information will have been submitted to the competent authority by the notified body?

As Ukraine celebrate multiple public holidays in early May, Cratia does not expect responses until May 20-25.

Eventually, Ukraine will likely harmonize with the new EU Medical Device and IVD Regulations, which will come into force over the next three to five years in Europe. *(Also see "The New World Of EU Regulation: Medtech Insight Editors Discuss How To Prepare And Avoid The Hurdles" - Medtech Insight, 15 May, 2017.)* But Cratia hopes for adequate time to assimilate the current changes, which are based on the Medical Device Directive and IVD Directive – set to be phased out in Europe – before the Ukraine authorities embark on another set of regulatory changes at the national level.

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Singapore Consults On Implementing New Device Distribution Standard

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Singapore's Health Sciences Authority has issued a new draft guideline to illustrate some of the approaches that companies can follow to implement and maintain a quality management system that conforms to the requirements of the Singapore Standard for Good Distribution Practice for Medical Devices – Requirements (SS GDPMDS).

Compliance with the standard is mandatory for importers, wholesalers and third party service providers dealing with medical devices and they must obtain GDPMDS certification before submitting their licensing application.

The SS GDPMDS is a new standard specifying requirements for a quality system for the handling, storage, delivery, installation, servicing and secondary assembly of medical devices. The standard was approved by the Biomedical Standards Committee on behalf of the Singapore Standards Council on Oct. 13, 2016, and it was first published earlier this year, said May Ng, of Singapore-based medical device consulting company, ARQon.

Before SS GDPMDS came into play, companies had been following – and still can follow – the technical specification TS-01(R2.1) on good distribution practice for medical devices, which will be phased out in three years.

But Ng told *Medtech Insight* that new companies entering the medtech distribution arena should use SS GDPMDS and not rely on TS-01(R2.1) as the latter will be scrapped by 2020. Existing companies, she suggested, should perform a "gap review" between SS GDPMDS and TS-01(R2.1) and prepare to transfer to the new Singaporean standard at the next available opportunity for GDP re-certification.

She explained that the responsibility of undertaking the gap review rests with the "management representative" – a member of the management team that is appointed to undertake the ultimate responsibility of ensuring, among other things, that the processes needed for the quality management system are established, implemented and maintained. Also, the gap review should be on the agenda of top management, who are required to review the company's quality management system at regular intervals to ensure it remains effective.

In its draft guideline to support the implementation of SS GDPMDS, the HSA says that the appointment of the management representative should be documented, for example in the site master file or on an official appointment letter. A deputy can be appointed to undertake the necessary responsibilities in the absence of the management representative.

Regarding management review, the draft guideline says that this should be undertaken at least once a year and the review records should contain, among other things, a description of any corrective or preventive action to be taken.

The draft guideline also contains advice on: the types of records that companies need to maintain and their retention periods;

personnel management; maintenance of premises and facilities; secondary assembly; traceability; dealing with counterfeit, adulterated, unwholesome or tampered medical devices; handling complaints; undertaking field safety corrective actions; carrying out internal audits; and outsourcing of activities.

Overall, Ng thinks that the draft guideline is a useful document for the industry as it supplements SS GDPMDS.

Stakeholders have until June 9 to comment.

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TGA Consults On Ground Rules For Identifying 'Comparable' Regulators To Reduce Duplication

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Australia's Therapeutic Goods Administration is inviting stakeholder feedback on its proposal to identify "comparable" overseas regulators on whose decisions it can rely on to support its device registration process. For starters, the TGA plans to evaluate regulators on the International Medical Device Regulators Forum's management committee – namely Brazil, Canada, China, Europe, Japan, Russia, Singapore, and the US – to ascertain whether their regulatory standards are similar to those in Australia.

By relying on marketing approvals granted by comparable overseas regulators, the TGA believes it can avoid duplication of work during the device registration process without comprising on patient safety. The TGA has drawn up a set of proposed criteria that would be used to identify comparable overseas regulators and to allow confidence in the assessments undertaken by such agencies or by third parties overseen by them.

The TGA clarified that its reliance on assessments issued by comparable regulators will vary and depend on the degree to which these overseas assessments can be "repurposed" to demonstrate compliance with the Australian regulatory framework. The agency explained that it wants to identify comparable regulators to either:

- Use approvals issued by them as evidence of regulatory compliance to facilitate inclusion of devices on the Australia Register of Therapeutic Goods; or
- Enable work-sharing to deal with applications lodged in parallel in two (or more) jurisdictions - the TGA said it was unlikely that work-sharing would be possible with EU bodies or other commercial bodies designated by regulators to undertake assessments because international co-operative agreements operate between government regulators rather than commercial organizations.

To rely on approvals issued by overseas regulators, the TGA would "map" these assessments to ensure safety, quality and performance were demonstrated to meet Australian requirements for compliance against essential principles. In addition, the TGA would check if the classification of the medical device was comparable to ensure that the rigor of the assessment was appropriate to Australian standards.

While such mapping would be fairly straightforward in respect of conformity assessment certificates issued by EU notified bodies given the close parallels between the Australian and EU medtech regulatory frameworks, the TGA noted that the extent to which this was practicable for assessments issued by other overseas regulators would vary based on several factors.

To use overseas approvals, the extent of the gap between the overseas approval and the additional information required by the TGA to establish compliance with the regulatory framework will be critical. If the gap is too extensive, it will be impractical to rely on the overseas approval "as the TGA would effectively be undertaking an abridged conformity assessment (without the corresponding fee)," the agency said. Such gaps, and how to bridge them, would have to be clearly articulated in guidance to allow companies to decide whether they should apply for product registration on the basis of such evidence.

In the case of work sharing, pre-submission discussion with the concerned regulators would be critical to establish their willingness to cooperate on the assessment, and to allow an appropriate abridgement of fees by one or both regulators, the TGA noted. The agency clarified that work sharing would only occur at the request of the company and would be subject to agreement by the comparable regulator, on an application by application basis.

COMPARABILITY EXERCISE

Assessing an overseas regulator against the comparability criteria and undertaking gap analysis to develop standard operating procedures and guidance will involve a significant investment of TGA resources. At this stage, the TGA expects that only overseas regulators that are members of the IMDRF's management committee would be evaluated.

The process would include, among other things, reviewing the overseas regulatory framework, including its objectives, processes, the requisite competencies to conduct assessments and the suitability of any outputs for use as objective evidence for decision-making. In addition, the TGA would analyze a sample of assessment reports issued by the overseas regulator.

Once an overseas regulator was assessed as comparable and the use of their assessments practically appropriate, they would be included as a 'comparable overseas regulator' in a list to be published on the TGA's website. Legislative changes to the Therapeutic Goods Act 1989 will be needed to enable this.

Stakeholders have until June 30 to comment on the TGA's proposal. Based on the outcome of the consultation, the regulatory amendments will be developed during 2017, for a scheduled Jan. 1, 2018, commencement.

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CONTINUED FROM PAGE 1

geted than traditional SCS systems and designed to achieve better outcomes, and reduce stimulation felt by patients, will be analyzed as part of the competitive landscape in part two of this pain management article series.

Hilary Fausett, a board-certified pain management specialist at the FootHill Center for Pain Management in Pasadena, California, who has extensive experience with SCS devices and also worked with industry giants Medtronic and Boston Scientific, told *Medtech Insight* that for many patients, SCS therapy is an "absolute miracle."

"If you think about it, just like with a pacemaker, now a doctor can program the sensations that the nerve interprets to send it up to the brain," Fausett said. She agreed that the next-generation systems have undoubtedly broadened the applicability for SCS systems, but said that it's up to the doctor to make the correct diagnosis and choose the correct device and stimulation for each patient.

Robert Bitonte, a specialist in physical medicine and rehabilitation with a subspecialty in brain injury medicine and health care attorney in downtown Los Angeles, finds that it's particularly exciting that these promising technologies are coming at a time that coincide with the public's, the legislature's and physicians' concerns about opioid use.

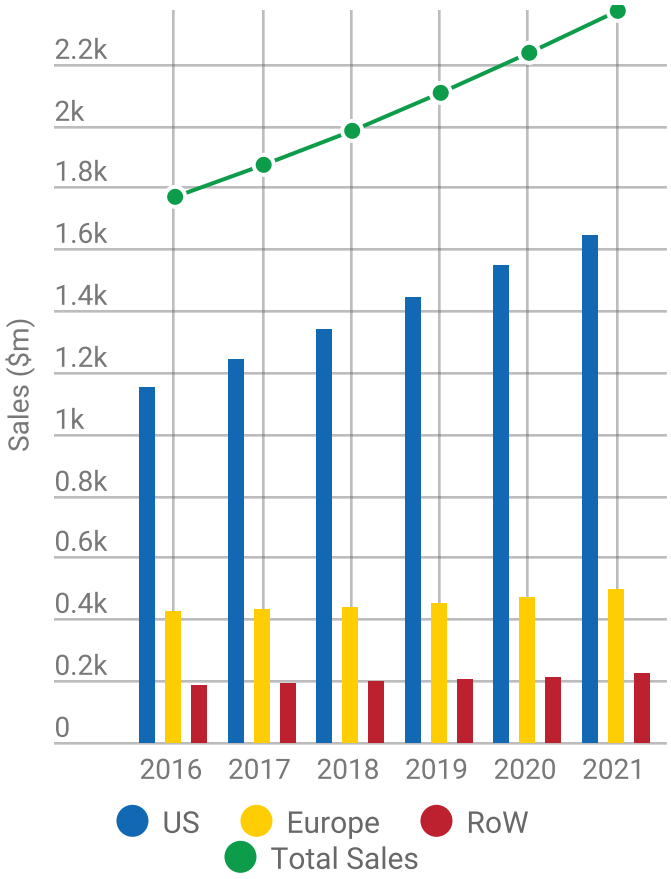
"Opioid use is still going to be important in pain management, but there is no question that there is increased scrutiny and legislation regarding opioids (that is) going to have a downward trend on the use of opioids," Bitonte told *Medtech Insight*.

Bitonte said his interest in SCS therapy is in referring patients, who suffer from failed back syndrome and complex regional pain syndrome, to specialists. He said that patients seem to respond well to SCS therapy and there's emerging evidence that it's very effective in complex regional pain syndrome as well.

"These two entities (failed back syndrome and complex regional pain syndrome) have been historically difficult to take care of and SCS seems to be an emerging and effective answer to both of these difficult problems," he said.

FIGURE 1

Spinal Cord Stimulators, Market Forecast, 2016-2021



Source: "Pain Management Devices Market," Meddevicetracker

SCS REGIONAL OUTLOOK: US DOMINATES

When it comes to the regional outlook for global sales of SCS devices, the US remains the dominant market, accounting for 65% of total SCS systems revenues in 2016. This is followed by European sales, which accounted for 24.3%, and countries outside Europe and the US accounting for 10.7%, according to the *Meddevicetracker* report.

The analysts expect the biggest growth will remain in the US where SCS systems sales will climb from $1.2bn in 2016 to $1.6bn in 2021, a CAGR of 7.4% This is driven by several factors, including the recent and anticipated regulatory approval of new SCS devices, the rising demand for pain management solutions from a growing aging and obese population and a growing interest in using SCS devices as an alternative therapy. Meanwhile in Europe, sales in this market will rise from $431m in 2016 to $500.6m in 2021, a CAGR of 3%. In the emerging markets, sales of SCS systems are expected to see modest growth from $189.3m in 2016 to $224.9m in 2021. (See Figure 1.)

GROWTH LIMITER: ONE-TIME REIMBURSEMENT

Currently, the wider, worldwide adoption of SCS systems is also being challenged on multiple fronts.

In the US, in particular, growth in the SCS systems market flattened after the Centers for Medicare and Medicaid Services (CMS) introduced a new physician reimbursement policy on Jan. 1, 2014 for

trialing SCS in the office setting, reducing payments by more than 70%, according to *Meddevicetracker*.

This caused a temporary disruption in the market with SCS systems volumes recovering and returning to mid-single-digit growth in 2015.

But for physicians who are using SCS systems, the reimbursement issue remains.

Fausett noted that in the US, Medicare or any other health insurance payer first needs to approve the trial of neuromodulation with an externalized power source; and if this trial proves successful, the payer needs to approve the subsequent permanent implantable long-term therapy.

She said the trial costs $1,500 for the piece of wire alone, excluding costs for booking the sterile room, needle, fluoroscopy and other costs associated with the surgery; and Medicare pays only once for the device, which can run between $20,000 and $50,000, depending on the features. The device typically lasts a decade.

By contrast, she pointed out, patients who live in countries with a national health care system such as Canada, England and Australia, can count on the government to cover the cost for the trial and the device.

What this means for US doctors, in turn, is that they need to ensure that the device absolutely works.

"A lot of insurance companies and Medicare will say they will pay for one device for a person," Fausett said. "If the equipment is not reliable, that's not good for the patient."

This makes it pertinent for doctors to know that the device they use is reliable, easy to implement, and won't cause irritation or other problems.

Hence, Fausett said, while it's exciting to see new technologies come to market, they need to pass the test of time.

"There is the risk of failure at various points," she said. "As you breathe, as you twist, as you bend, this device must have enough give in it so it can move – it will move with you – but not so much give in it that it migrates and moves to a part of the body that doesn't provide the pain relief."

She said it is critical for doctors to have good relationships with manufacturers, because there are issues that can arise. She offered these examples: "Sometimes it's not just the electrical stimulation and what's called the lead that's important, but there is the anchoring device. How do you keep it in place? Will it scar into place or will it cause such a reaction in the body that there is so much scar tissue formed that it can be actually dangerous."

In the US, in particular, many doctors see SCS systems as a viable alternative to help cut down on the opioid epidemic, but some argue that the US health-care system has ignored this alternative treatment because of the high up-front cost of the procedure.

COST-BENEFIT RATIO

Timothy Deer, president of the International Neuromodulation Society (INS) and president and CEO of the Center for Pain Relief in Charleston, West Virginia, told *Medtech Insight* there is the hurdle for governments and health insurance companies to understand the cost-benefit ratio. He added that studies have shown that neuromodulation systems are very cost-effective therapies.

"While there is an initial cost, over time, the reduction in other costs like drugs and other therapies have shown to be much more beneficial with neuromodulation, whether it be intrathecal drug delivery, SCS, brain stimulation, incontinence treatment – the government affairs have to realize, over the long term, they will save a lot of money," Deer said. *(Also see "INS 2017 Aims To Offer Sneak Peek Into Future Neuromodulation Trends" - Medtech Insight, 18 May, 2017.)*

Bitonte said there is always going to be emerging technologies, and replacing the older technology is one issue; but, he noted, "Only practitioners that are out there doing hands-on work will be able to tell you when it's time to move on to a newer technology."

And even if the technology is proven to work, and there is an established need, it won't get into patients until it is deemed "medically necessary" by payers, he emphasized. He foresees that the medical community will need to advocate for newer SCS technologies and legislators will need to push for it, because of the increased scrutiny about opioids and the reluctance by physicians to use opioids.

Deer agreed by saying that just as payers need to understand the value of SCS systems, doctors have a responsibility to select the right device for each patient, saying "cost-effectiveness improves, if the patient selection does." *(Also see "St. Jude: Neuromodulators Could Be Key To Fighting Opioid Epidemic" - Medtech Insight, 16 Nov, 2016.)*According to an article that appeared in the *Journal of Pain Research* last July, there are a number of studies that consider the economic factors associated with SCS. The studies suggest that despite significant initial cost, SCS compared to conventional treatments, result in long-term reductions in health care costs and offset upfront cost. Most of the studies appear to have been conducted in countries such as Canada and the United Kingdom, not the US.

THE NEED

All three physicians agreed that SCS systems are currently underused in the US. Fausett said that many consumers don't know about the existence of such devices, and when they learn about it, the idea of having a permanent device implanted into their bodies can also be frightening.

"People get so afraid of having something in their body," Fausett said. She said many patients think they can simply tolerate the pain, not realizing that they can cause permanent damage by not addressing the problem. She said with the correct SCS systems, quality of life can be drastically improved.

"They're walking better, moving better, rather than neglect that part of the body, they can get stronger," she said.

Bitonte agreed. "Whenever you put into your body (something) that is coming from outside that is going inside, there is obviously risk to it," he said. "We are talking about a changed environment, a need for something, neuromodulation seems to be at least one evolving, promising effective modality to do that."

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WannaCry Cybersecurity Alert Shows Medtech Software Must Look Beyond Quick Fixes

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The WannaCry (WanaCrypt0r 2.0, WCry) ransomware attack that affected over 200,000 systems globally on May 12 locked users out of their IT systems and demanded a relatively small bitcoin ransom to let them resume access.

Most of the headlines focused on the relatively large effect on systems used by the NHS England, where 40 trusts reported that they had been hacked. Eleven Scottish Health Boards were also affected. Patient data were not affected: files were not compromised, simply inaccessible. Clinical care was affected and logistics disrupted.

This was a problem largely of the national UK health provider's own making – the persistent use of unsupported systems using outdated Windows XP systems, and failure in some cases to upload security update patches when prompted to do so or in time.

NHS Digital counters that the vast majority of NHS organizations are running contemporary IT systems, but attributing blame to provider systems' inadequate budgets is a pointless exercise after the fact. The lessons are there to be learned at provider systems around the world, which will be aware that the hacking could have been much more damaging. They should use the incident to protect their own systems from risk of compromise.

For their part, medical device industry suppliers were quick to help providers restore operations and protect systems from further risk of attack. Microsoft issued a patch to users a few days after the attack, but some NHS IT developers are recommending the health service reduce its reliance on Microsoft.

The exploitability of any such vulnerability depends on the configuration and deployment environment of each product. For the device industry branches most affected by the hack – digital pathology, and CT and MRI imaging, the solution is not as easy as simply applying a patch at will. That reality is explained by AXREM, the UK trade association representing suppliers of diagnostic medical imaging, radiotherapy, health care IT and care equipment, in a release issued on May 18.

Medical imaging systems differ from standard personal computers and server systems that can often receive cumulative updates or patches promptly. But medical imaging system software products are medical devices, and the strict regulatory needs mean that suppliers must do rigorous tests on each and every software update to ensure that functionality and safety are not compromised.

"For this reason, the reliance on the provision of clinical product software patches for defending against malware attacks is not a sustainable option, given that this would mean a new regulatory-approved and clinically-tested software release for multiple assets on as much as a daily or weekly basis to keep pace with evolving malware," says AXREM.

Shutterstock: Kayasit Sonsupap

Suppliers are having to balance their obligation and responsibility to validate patches and software updates, as well as provide additional network security provisions, with the requirement to promptly apply appropriate protective measures in addition to those applied within customers' own networks.

The significance of the May 12 incident is that it is a health care first in terms of its scale and impact. At the same time, few could deny there was a pervading sense of the inevitability of such an episode. Cybersecurity has rapidly become a top priority in the device industry; in March 2017, day two of the International Medical Device Regulators Forum (IMDRF) meeting put a major focus on the theme of understanding and tackling the cyber threat to the medical device industry.

Late last year, DITTA, the Global Diagnostic Imaging, Healthcare IT, and Radiation Therapy Trade Association (DITTA), released a white paper on cybersecurity needs. "Cybersecurity of Medical Imaging Equipment" set the tone for what will be this industry sector's major talking point for the whole of 2017 and beyond.

Post WannaCry, NHS Digital provided more guidance on protection against cyberattacks, but manufacturers know that the ball is in their court and they must devise solutions with the regulatory constraints they live under not just for their own products but for their downstream customers.

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Abbott Catheter Recall Designated As Class I

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Abbott Laboratories Inc. is recalling some coronary catheters because of a mechanical problem that's been linked to 19 injuries and one death. US FDA designated the action as a class I recall, which means the problem poses a reasonable likelihood of serious adverse events or death, on May 19.

The device-maker first told providers about the voluntary class I recall via a March 22 field safety notice, which asked customers to return any affected devices to Abbott unused.

Recalled balloon catheters include *Abbott NC Trek RX*; *Abbott NC Traveler*; and *Abbott NC Tenku RX PTCA* units manufactured between Jan. 1, 2015, and Jan. 2, 2017, and distributed between Jan. 1, 2015, and March 14, 2017. The recall affects 449,661 units worldwide, FDA says.

The adverse events cited in the recall were all related to problems inflating or deflating the balloon. If too much force is used to remove the protective balloon sheath, the balloon becomes more difficult to inflate or deflate. This could cause problems including air embolism, thrombosis, heart attack and death, FDA says.

The one death, Abbott says, occurred after a patient suffered multiple surgical complications following surgery to remove a balloon that wouldn't deflate.

The tight sheath issue has been reported in about 0.12% of the coronary catheters sold worldwide, Abbott says.

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New Acquisition And Positive Data Inflates Philips' Respiratory Biz

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Royal Philips Electronics NV has struck a second M&A deal for its sleep and respiratory care business this year, with the acquisition of **Respiratory Technologies, Inc**. (RespirTech), the US developer of the *inCourage* airway clearance vest therapy for chronic respiratory conditions. These conditions include chronic obstructive pulmonary disease (COPD) and cystic fibrosis.

The inCourage vest is worn by the patients and is attached to a machine that creates compressions to the chest, helping to loosen, thin, and move mucus through the lungs. RespirTech's website explains that while other airway clearance vests can squeeze a patient's chest like a blood pressure cuff and make it hard to take a deep breath, the inCourage vest has "active venting" which uses a lower operating pressure to allow the chest to easily expand for a deeper and more comfortable breath during therapy.

St Paul, Minnesota-based RespirTech was founded in 2004 and has grown to an organization of around 210 employees.

The technology is aligned with Philips' strategy to focus more on out-of-hospital, home-based care therapies. The group's sleep and respiratory care unit is a star performer within the Personal Health division of Philips Healthtech, reporting high single-digit revenue growth in the first quarter of this year, and profitability that is above average for the division.

"RespirTech's offerings further enable Philips to accelerate its growth in respiratory care, especially for COPD patients with bronchiectasis, an often underdiagnosed and undertreated comorbidity. Moreover, RespirTech's portfolio includes a robust clinical support program for managing respiratory patients in the home," Philips stated. The firm added that the deal will support "Philips' ambition to deliver cost-effective, clinically focused service programs, such as its sleep-focused Patient Adherence Management Service, which enable health providers to better manage their patients."

The RespirTech acquisition is Philips' second investment in its sleep and respiratory care unit; in March, it acquired Australian Pharmacy Sleep Services to accelerate its home sleep testing offering through the pharmacy channel in Australia.

BREATHE EASIER AT HOME

Separately, and providing further support for home-based respiratory care solutions, Philips announced that a five-year, randomized clinical trial in the UK has demonstrated that in-home noninvasive ventilation (NIV), in conjunction with home oxygen therapy, led to significant delay in hospital readmissions for COPD patients.

Results from the 116-patient study in the UK showed that the addition of home NIV to oxygen therapy prolonged the median time to readmission or death from 1.4 months to 4.3 months, and also improved quality of life in the first six weeks.

Preliminary results from this trial were announced in September 2016 at the European Respiratory Society's International Congress in London and more recently at the American Thoracic Society International Conference in Washington, DC (May 19 – 24).

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EuroPCR 2017: Robocath Eyes H1 2018 Robotic Catheterization System Launch With New Funds

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Robocath is set to embark on safety and efficacy studies of its *R-one* robotic catheterization system, supported by a fresh injection of funds from both new investors and existing shareholders. The €4.7m ($5.2m) round – led by M Capital and Normandie Participations, contributions from past investors Go Capital and NCI – will not only help see the company through the regulatory pathway, it should also take the French firm beyond the anticipated H1 2018 market launch of the technology and to the end of next year, Robocath CEO Pascal Guy told *Medtech Insight*.

Photo credit: Robocath

News of the financing was announced during of the annual EuroPCR meeting, in Paris May 16-19, where Robocath is showcasing R-one. Guy said that with EuroPCR being the one of the two biggest cardiology meetings in the world, and with the company being "relatively close to CE marking and market launch, this is an opportunity for us to use this event as a starting block and prelaunch our system."

The R-one system is designed to perform interventional cardiology procedures, such as balloon catheter angioplasty and stent placement. It consists of a console, from which the physician will use two joysticks – one for controlling the catheter, the other the guidewire – to remotely manipulate a robotic arm that handles the guidewire and catheter at the operating table. The console also has monitors that allow the physician to track the patient's vital parameters and to obtain radiographic images of the guidewire and catheter inside the patient, while the lead shield on the console provides the physician protection from X-ray exposure.

Robocath was founded by the firm's current chairman, Philippe Bencteux, a neuroradiologist who has been working on R-one's platform technology for a little over a decade. Guy told *Medtech Insight* that his company has tried to make the R-one system simple and intuitive to operate. "It's what we call an anthropomorphological technology; it is able to reproduce the movement of the human hand. So when the robotic arm is manipulating the guidewire and catheter, it can move forward and back, with rotation clockwise and anti-clockwise. It's really reproducing all the movements that an interventional cardiologist would make during the procedure," said the CEO.

Additionally, the proprietary SecureAccess feature that has been incorporated into the R-one system allows the guidewire catheter to be simply clicked onto the robot in "tenths of a second", and ensuring the catheter remains still throughout the procedure so as to prevent loss of access to the lesion. "This is an important feature because in interventional cardiology procedures, there is the risk of losing access if the guidewire and catheter moves and you have to start again and re-access the lesion. This would never happen with R-one because the guidewire of the catheter is always locked and secured due to our SecureAccess technology," Guy said.

Currently, there is one robotic system on the market for use in interventional cardiovascular procedures: **Corindus Vascular Robotics Inc.**'s *CorPath* was first cleared by the US FDA in 2012 and the second-generation system, *CorPath GRX*, was cleared in October last year and is now being commercialized. Sales of this rival device, Guy said, is largely focused in the US, and Corindus does not have a presence in Europe, where Robocath will be first targeting with R-one. He believes that R-one's advantages over CorPath includes its simplicity and intuitive ease-of-use, as well as its anthropomorphological feature. "[CorPath] cannot reproduce human hand movements like our technology does. It also has a lot of moving parts and is more complex to use, whereas we have been very keen to offer the cardiologist an extremely easy to use technology with a very short learning curve. We've had surgeons that have used the system on animals, and usually within 2-3 cases, they become really comfortable with the system," said Guy.

Pending CE-mark approval of R-one, Robocath intends to adopt a hybrid commercialization model, going direct in certain territories, while using distribution partners for others. In addition to Europe, the company will also be targeting the Middle East.

Further down the line, in 2019, Robocath also intends to launch its second-genera-

tion system. While the current generation of R-one is designed to accommodate rapid exchange devices, the second-generation system will be designed for both rapid exchange and over-the-wire devices. "The first-generation R-one will be targeting the cardiologist as almost all procedures in interventional cardiology is rapid exchange. But in peripheral vascular and neurovascular interventions, they are still working with over-the-wire devices, so the second-generation R-one will allow us to expand into other indications," said Guy.

With the upcoming safety and efficacy study, Robocath will also use the trial to document how well the use of a robotic system like R-one – which these interventional procedures to be performed remotely and outside of the radiation risk zone – is at protecting the physician and staff from X-ray exposure." The beauty of a system like this is that it takes care of the needs of healthcare professionals who face significant challenges of being exposed to radiation," Guy said. "There is a possibility for us to bring more safety and comfort to their workplace. But it is also in the interest of the patient and health care payer. If you can reduce the pathologies caused by radiation exposure, it will have an impact on health economics too. So, we are working on this health economics aspect as it will have an important factor in our future success."

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EuroPCR 2017: Xeltis' Regenerated Heart Valve Shows Promising Early Preclinical Data

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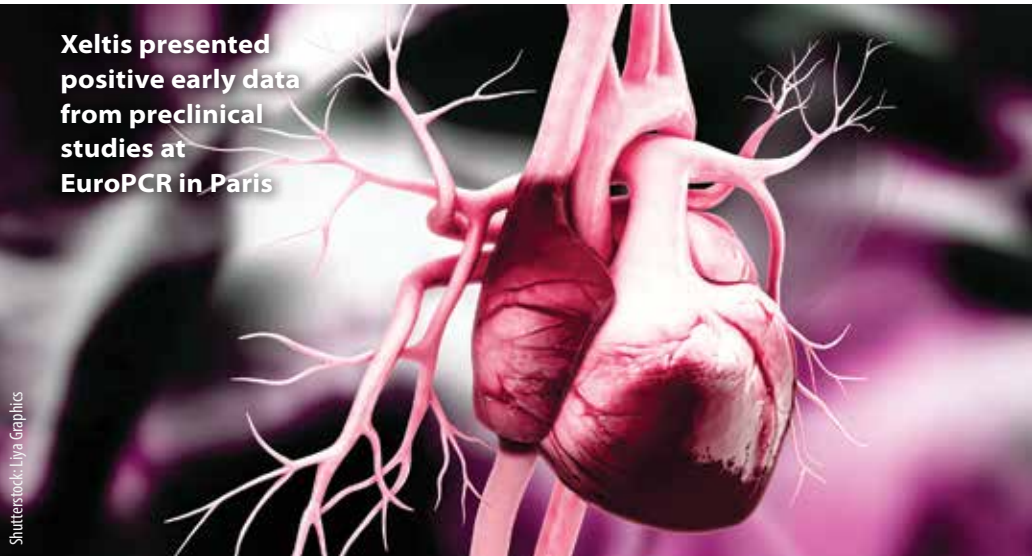

Xeltis presented positive early data from preclinical studies at EuroPCR in Paris

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Emerging structural heart disease specialist Xeltis has presented positive early data from preclinical studies that showed its bioabsorbable aortic heart valve implant was "fully functional" *in vivo* six-months after implantation. These results were presented at a dedicated plenary session on bioresorbable valve therapy at EuroPCR on May 17 in Paris.

Laurent Grandidier, CEO of Xeltis told *Medtech Insight* the results were "very encouraging and positive."

"We have a lot of excitement from preeminent physicians who are involved in this developmental program. The results show the valve has good hemodynamic performance and is functional at six months in animals," he said.

Xeltis' transcatheter aortic valve implant uses the company's Endogenous Tissue Restoration (ETR) platform technology that enables patient's bodies to naturally rebuild heart valves and work as a normal heart valve once implanted. Patients form new tissue around and inside the device, developing a new, functioning heart valve. The restoration process is enabled by the porous structure of Xeltis' heart valves, which are made of bioabsorbable polymers. As ETR occurs, Xeltis' implants are gradually absorbed by the body.

Grandidier said: "The objective of our technology is to get rid of all the downsides associated with standard heart valves. Existing artificial heart valves are generally made of animal tissue that are treated chemically in order to remove all the pathogens. But the problem with these animal tissue-derived valves are that they create a chronic inflammatory response for the body which ultimately leads to the deterioration of the valve over time."

"Essentially all of today's valves have these durability issues. There are all kinds of problems linked with the usage of animal products. Heart valve manufacturing is structured manually and its complicated, cumbersome and very expensive. From our experience and data, we are seeing that once our valve is absorbed, you remove the triggers of this chronic inflammatory process." Grandidier said the data was promising as traditional valves would already show signs of structural valve deterioration after six months.

In addition to its transcatheter aortic valve, Xeltis' initial product - a pulmonary valve replacement *RestoreX* has al-

ready been tested in-humans. Two-year follow-up data for a pediatric feasibility study of RestoreX were presented last year at the EACTS 2016 annual meeting. Five patients, aged 4 to 12 years, with only one functioning heart ventricle as a result of congenital heart defects, were treated with Xeltis' graft. The one- and two-year data showed "positive functionality" results, absence of device-related adverse events, and significant improvement in patients' general conditions. *(Also see "Clinical Corner: New Data From Xeltis Bioabsorbable Heart Repair Devices Headlines Trial News" - Medtech Insight, 6 Oct, 2016.)*

The Swiss-Dutch company has begun enrolling patients into a multicentre feasibility clinical trial "Xplore-I" for pediatric patients from 2 to 21 years of age. The aim of the clinical study is to assess the survival rate of patients at six months following implantation of the bioabsorbable Xeltis pulmonary valve.

In January, the US FDA approved an Investigational Device Exemption (IDE) for Early Feasibility Study (EFS) to implant Xeltis pulmonary valve in 10 patients. This Xplore-II study is expected to begin later this year. The FDA also granted Humanitarian Use Device (HUD) Designation for Xeltis' pulmonary valve as a bioabsorbable pulmonary heart valve for the correction or reconstruction of right ventricular outflow tract (RVOT) in children.

Xeltis closed an extended Series B financing a couple of years ago, raising

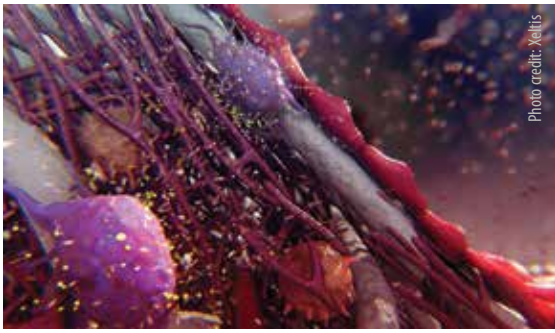

Photo credit: Xeltis

$33m in total (initial $30m in 2014, extended to $33m in 2015) led by Dutch investors Life Science Partners (LSP) and Kurma, a French fund. Grandidier said Xeltis is currently exploring "various options" for future fundraising.

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STARTS & STOPS:

New Trial Starts Led By Peripheral Vascular Interventions

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Trials of cardiovascular devices, including peripheral interventions, are highlighted in this month's edition of Starts & Stops, *Medtech Insight*'s regular feature on medtech clinical trials that have started, restarted, completed, or terminated.

Mercator MedSystems Inc. announced April 26 that the first patient has been enrolled in the TANGO (Temsirolimus Adventitial Delivery to Improve Angiographic Outcomes Below the Knee) clinical trial of its *Bullfrog* micro-infusion device for the adventitial delivery of Torisel (temsirolimus) after revascularization of lesions below-the-knee peripheral artery disease in patients with critical limb ischemia. Tango is a randomized dose-escalation trial designed for about 60 patients with critical limb ischemia related to arterial obstructions.

TANGO is the fourth ongoing clinical trial of Bullfrog to treat below-the-knee peripheral artery, and the third in the US. *(Also see "Mercator Moves To New Studies Following DANCE Success" - Medtech Insight, 11 Oct, 2016.)* Torisel, marketed by Pfizer, is an anti-proliferation drug in the limus family intended to reduce restenosis. According to Mercator, Medtronic *IN.PACT 0.014* paclitaxel-coated percutaneous transluminal angioplasty is the only other intravascular drug-delivery device in a US clinical trial for treatment of below-the-knee peripheral disease. *(Also see "Starts & Stops: Boston Scientific Starts, Stops, And Finishes TAVR Trials" - Medtech Insight, 14 Mar, 2017.)* Bullfrog is unique in that it delivers an anti-proliferative agent locally to below-the-knee lesions without leaving behind a permanent implant, and is more suited to navigating the tortuous

anatomy of below-the-knee vessels than balloons, according to Mercator.

During its first-quarter earnings call on April 27, **Boston Scientific Corp.** announced that the start of the RANGER II SFA trial, which is designed to support regulatory US and Japanese regulatory submissions for the *Ranger* paclitaxel coated balloon for treating lesions in the superficial femoral and proximal popliteal arteries. Ranger already has a CE mark. *(Also see "Market Update: Growth And Opportunities In Peripheral Artery Disease" - Medtech Insight, 18 Feb, 2016.)*

On May 10, **Avera Pharmaceuticals Inc.** announced the US FDA approved its plan to start first-in-man clinical trials of its *Natural Vascular Scaffolding* drug/device combination for the treatment of peripheral vascular disease. NVS is a delivery device that uses light to activate a drug that creates a new natural structure that keeps the blood vessel open. The trial will begin at three US centers this summer. Sioux Falls, SD-based Avera plans to market NVS through **Alucent Medical**, based in Salt Lake City.

Among the other high-profile cardiovascular devices entering trials in the last month is **REVA Medical Inc.**'s *Fantom* bioresorbable stent. Fantom is being evaluated in 50 patients in Germany with complex disease including multiple vessels and long lesions in an extension of the FANTOM II trial. The primary endpoint for this arm of the trial is major adverse events at six months. Fantom recently earned a CE mark based on results from the first part of FANTOM II, which showed a 2.1% six-month major adverse event in 240 patients. *(Also see "OUS Approvals Analysis: Small Companies Dominate International Approvals In April" - Medtech Insight, 9 May, 2017.)*

Corindus Vascular Robotics Inc. announced May 15 that it has launched the PRECISION GRX post-market registry to continue market surveillance of its second generation *CorPath GRX* robotic percutaneous coronary angiography system, which offers improvements in procedural control, enhanced workflow and radiation protection compared to the CorPath 200 system. The PRECISION registry showed high rates of clinical and technical success rates with CorPath 200 in 754 patents and a total of 949 lesions. Ehtisham Mahmud of the University of California - San Diego presented the results at the EuroPCR meeting in Paris on May 12.

The FDA-approved STEMI Door to Unloading (DTU) Study of **Abiomed Inc.**'s *Impella CP* heart pump has begun, the company announced May 4. The trial will evaluate the feasibility and safety of unloading the left ventricle using the Impella CP heart pump prior to primary percutaneous coronary intervention in patients presenting with ST segment elevation myocardial infarction without cardiogenic shock.

The trial will randomize up to 50 patients to ventricular support with Impella CP with immediate primary percutaneous coronary intervention, or to Impella CP placement with 30 minutes of unloading prior to primary PCI. All patients will undergo cardiac magnetic resonance imaging to the reduction in infarct size following the intervention and the primary endpoint will be adverse cardiovascular and cerebrovascular events at 30 days.

Cardiovascular trials are among those recently terminated. Medtronic has terminated the ENABLE I non-interventional post-market study, which was the post-market long-term follow-up study of the 148 patients in the investigational study of the ATS 3f Enable aortic bioprosthesis. Medtronic retained the right to terminate the observational study at any time after the five-year follow-up. The patients were originally recruited from 2007 through 2009 and results published in 2014 following an average of 2.76 years and a total of 388.7 represented the longest follow-up study for a sutureless bioprosthesis. In the 24 patients who had reached the five-year follow-up at that point, 93.8% were freed from valve-related mortality and 95.4% were free from reoperation.

In the in-vitro diagnostics space, **Biocept Inc.** and the Addario Lung Cancer Medical Institute in San Carlos, California have initiated the 400-patient ALCMI-009 liquid biopsy clinical trial of Biocept's *Target Selector* assay platform to detect and assess cancer biomarkers found in both circulating tumor cells and circulating tumor DNA from lung cancer patients.

Also, **OncoCyte** announced during its April 28 earnings call that its breast cancer liquid test is developing ahead of schedule, and has entered a multi-center study to further develop and verify the results of the earlier studies. OncoCyte's pipeline breast product is intended to be used in lieu of biopsy for "suspicious mammograms" with a high degree of accuracy.

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CLICK

TFor details of trial suspensions, initiations and completions reported between April 21 and May 20, 2017, go to http://bit.ly/2q0xBB0.

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