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New-Gen Devices Offer Sleep Apnea Patients Alternative CPAP Routes

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Obstructive sleep apnea (OSA) is a common, devastating and costly condition. It affects an estimated 100 million people worldwide, of whom 18 million are in the US alone, and its societal costs are huge. A 2010 joint Harvard Medical School-McKinsey & Company report estimated that the annual cost of moderate to severe OSA in the US is between $65bn-$165bn, including diagnosis and treatment, hidden health-care costs (notably cardiovascular disease, with which moderate to severe OSA is strongly associated), traffic and workplace accidents, and absenteeism.

For decades, the go-to treatment for moderate to severe sleep apnea has been for the patient to wear a continuous positive airway pressure (CPAP) device during sleep. (Market dominators for CPAP are **ResMed Inc.** and **Philips Respironics**.) These provide pressurized air on both inhalation and exhalation that keeps the airway open; it is highly effective, thus reducing the number of apneic episodes. But compliance is low. The device is noisy and cumbersome, and many people find it too uncomfortable to tolerate. One 2013 study estimated that 46%- 83% of patients prescribed CPAP use it less than recommended.

"CPAP works very well if you can tolerate it," says Matt Vaska, CEO and chairman of **ApniCure Inc**. "But there are huge numbers of people becoming noncompliant."

Those undertreated people are among the targets of OSA device start-ups. The global OSA market was estimated in a 2014 report from Transparency Market Research to be worth $3.8bn in 2012, rising to $6.4bn in 2019 at a CAGR of 7.8% between 2013 and 2019, according to *Sleep Review*. OSA diagnoses are on the rise, driven in part by obesity rates and increased physician awareness, even as some 80% of Americans with OSA remain undiagnosed.

Despite the clear need and profit promise, the space has seen high-flying failures in recent years. For example, **Apnex Medical Inc.** a Twin-Cities based startup, intended to develop an implantable OSA device. It raised $50m in venture capital, but folded in 2013 after an unfavorable clinical trial.

"It's a much tougher problem than people think," says John Stevens, a cardiac surgeon-turned-venture capitalist with **Headwaters Capital Partners**. "To solve efficacy and patient comfort, those are really big deals."

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Philips, Masimo Bury Hatchet Over Patient-Monitoring Battle

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The seven-year legal battle between Philips and Masimo has ended, with the two adversaries agreeing to drop all litigation and move forward with a wide-ranging sales and marketing, as well as technology integration, partnership.

Masimo, best known for its noninvasive pulse oximetry technologies SET and rainbow, was first to file the lawsuit against Philips in 2009, claiming the latter had infringed two Masimo patents. The litigation grew in complexity with claims and counterclaims from both parties, so much so that the court decided to handle the litigation in three phases. The first phase was tried in September 2014 and Masimo prevailed, with the jury finding Philips guilty of infringement and demanding that the Dutch group pay Masimo $467m in damages.

The second and third phase of the litigation was to have been tried in 2017, according to Philips' Steve Klink, but these will no longer go ahead – nor will Philips have to pay the $467m damages – in light of the two parties having now reached a truce.

Instead, Philips will make a one-off cash payment of $300m to Masimo in the fourth quarter of 2016 and the two companies will co-invest in certain marketing and product integration activities over the coming years. Philips will offer Masimo's noninvasive sensor technologies, including SET and rainbow, together with the Philips patient monitoring platforms in North America and in certain markets in Asia and Europe. This is the continuation of an existing agreement between the two companies.

Additionally, the two companies will work together to integrate other Masimo sensor technologies, such as SedLine brain function monitoring, O3 regional oximetry and Nomoline capnography technologies, in certain Philips IntelliVue monitors.

The relationship between the two had not always been sour; they have been business partners since 2004, with Philips offering Masimo's SET and rainbow technologies as "a plug-in" to Philips patient monitoring installed base, said Klink. However, there was "a bit of overlap" between Philips' and Masimo's portfolio which led to the legal dispute kicking off. "These past few years, it has not been easy, to say the least, to be business partners on one end and opponents in a court case on the other. So we decided to stop this litigation once and for all."

Philips said that the business partnership agreement with Masimo will have "minimal impact" on earnings in the fourth quarter of 2016.

Masimo is expecting to get a small boost to its bottom line from saving on legal fees. It now anticipates fiscal 2016 earnings per diluted share to go up one cent to $2.14.

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Third Expedited Approval Pathway Coming To China In January

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A third expedited approval procedure for medical devices will soon be available in China after regulators confirmed they would be introducing a priority-review designation pathway on Jan. 1, 2017.

The new priority-review and approval procedure is substantially the same as that which was proposed and issued for consultation in June, in that it will apply to devices that fall under national priority areas (group 1 devices) or address unmet clinical needs (group 2 devices), said Steven Wen, director of China Operations at consultancy company Brandwood Biomedical.

As well as applying to these two categories of devices, the new pathway will cover a third group of devices whose manufacturers are able to provide a rationale for a request for prioritization, Wen told sister publication *Pink Sheet*.

"I expect a lot of companies will try this pathway," Wen said. The request is free and it is simply a matter of making the request as part of a traditional regulatory submission, which, if successful, results in priority processing, he explained.

It is not yet clear how much time companies with priority review designation will save compared with China's standard device approval pathway.

"It is hard to predict at this moment because we don't know how many devices will be put into the prioritized pathway," Wen said. "Roughly speaking, you can save the waiting time of first round of review (90 working days for class III, 60 working days for class II) in the normal pathway, and 20 working days in the final administrative approval."

China Food and Drug Administration intends to evaluate prioritization requests for group 1 devices within five working days of accepting the submission, Wen explained. Group 1 devices are technologies that have been identified at the state level as nationally important in terms of scientific R&D, he clarified, adding that applicants would have to submit proof of state government prioritization.

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Group 2 submissions will be considered during a monthly CFDA panel review and applicants will be notified of the outcome after each panel meeting, Wen said. Group 2 devices are those that provide significant clinical advantages in the diagnosis or treatment of, for example, the following areas of unmet need: rare diseases; cancer; and diseases in the elderly or in children.

Group 3 devices will also be considered during monthly panel reviews, Wen said.

CHOOSING THE RIGHT PATHWAY

As for the two other expedited approval pathways already available in China, there is an accelerated approval pathway for devices applicable to emergency public health incidents and a fast-track approval mechanism for innovative devices.

"Companies need to assess their device situation then choose the best approach," Wen said.

The intentions and criteria of the priority review and innovative device pathways are different, he explained. The innovative device pathway, for instance, offers specific technical and regulatory assistance to applicants, parallel classification reviews, and a nominated internal champion to ensure smooth passage through the review.

Some cases might quality for both pathways, while others will not, Wen said. "I think some companies may try [the] innovative pathway first, because they have to raise the request before the submission. If it fails, they might try the prioritized pathway." Another critical consideration, he added, is that "the innovative pathway means you must do a clinical study in China." This might not be the case for the prioritized pathway.

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Two-Year Medical Device Reporting Window Retained In New FDA Final MDR Guidance

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US FDA has clarified its current thinking on Medical Device Reporting in a new final guidance that allows manufacturers to continue using a so-called "two-year rule" that lets them stop sending MDRs to the agency if there are no additional product problems after 24 months.

Overall, the guidance released on Nov. 8 is a roadmap for how firms should structure MDR programs to ensure they're submitting all pertinent information under FDA's MDR regulation (21 CFR, Part 803).

The document finalizes a draft from July 2013 that was stripped of the two-year MDR-reporting window; the draft instead instructed firms to seek exemptions from the agency to cease reporting, raising the ire of some in industry who said FDA would be inundated with exemption requests and that the requests would overly burden manufacturers.

The final document replaces an MDR guidance that has been used by industry since 1997. That document included the two-year rule.

After a product fails, there is a presumption that the problem will occur again "until either the malfunction has caused or contributed to no further deaths or serious injuries for two years, or the manufacturer can how through valid data that the likelihood of another death or serious injury as a result of the malfunction is remote," the new guidance reads. At the end of two years, FDA recommends that manufacturers submit a notification to the agency with a "summary of the data and the rationale for your decision to cease reporting."

The guidance points out, though, that firms "can request an exemption … from further reporting sooner than two years if your analysis of the data supports your conclusion that the malfunction has not caused or contributed to further deaths or serious injuries, and that the likelihood" of deaths and injuries happening is determined to be remote.

Although the two-year rule has been retained, the document nevertheless seeks MDR reporting exemptions from manufacturers for two types of situations.

First, companies and their contract manufacturers would have to come together to submit exemption requests to clarify which of the two will oversee MDR reporting. That is a change from current industry practice, wherein reporting responsibilities are designated in written agreements between the parties – and without FDA input.

"If Firm A and Firm B decide that they want only Firm A or Firm B to file the reports for the device, then the firm seeking the exemption must submit a request to us for an exemption from filing," the guidance states. "We recommend that the two firms submit a joint request specifying which firm will submit the reports."

Second, the document notes that a firm should file an MDR exemption request after it sells a 510(k) to another manufacturer. This language is not found in the 1997 document.

Sec. 4.12.2 of the document states: "Although Firm B is responsible for reporting adverse events for the devices it manufactures after it purchases the 510(k), Firm A remains obligated to report adverse events for the devices it manufactured. Firm A should … request an exemption from FDA to end its MDR reporting obligation for the devices it manufactured."

Aside from explaining when exemptions are needed, the guidance answers a litany of more basic questions, including those related to when a firm "becomes aware" of an MDR-reportable event, what is meant by "causing or contributing" to a death or serious injury, and the type of form that should be used when submitting reports.

It also answers meatier questions about what happens when a device is no longer marketed, how firms should treat reports related to medical interventions, and whether reports based on literature should be reviewed.

MDR-Reportable Events

The new guidance explains that "'MDR-reportable events' are events that manufacturers become aware of that reasonably suggest that one of their marketed devices may have caused or contributed to a death or serious injury, or has malfunctioned and the malfunction of the device or a similar device that they market would be likely to cause or contribute to a death or serious injury if the malfunction were to recur."

"Although the two-year rule has been retained, the final guidance nevertheless seeks MDR reporting exemptions from manufacturers for two types of situations.

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New Barrier For UK's Brexit Plans; Industry Looks For Potential Opportunities

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The Nov. 3 legal ruling that the UK government does not have the right to trigger Article 50 to begin the formal two-year process of taking the UK out of the EU without the approval of Parliament means even more uncertainty for the life-sciences sector.

The decision by the High Court of England and Wales could feasibly delay Prime Minister Theresa May's plan to invoke Article 50 by the end of March 2017. It is impossible to say at this stage how a potential delay will affect the impact of the UK's departure from the EU on the medtech industry.

Brian Kelly, a partner at the law firm Covington & Burling, said the judgment presented "an opportunity for individual companies and the industry to engage with members of Parliament to ensure that their views are heard before a vote takes place."

In a communication issued on Nov. 3, the Association of British Healthcare Industries said it still had "little clarity as to how negotiations with the EU will proceed, and, indeed, what type of relationship we want." ABHI said that the court's decision meant "continued uncertainty over the near-term." That said, the association is focusing its Brexit activities on the opportunities that leaving the EU may provide and, to this end, several of its policy groups are working to identify these opportunities and how it can make the most of them. Recommendations from the groups will focus on five areas: trade, regulation, manufacturing, investment and growth, and health system collaboration.

A Brexit steering group led by ABHI chair Phillip Kennedy will oversee the work of the groups.

The ABHI noted its involvement in the UK EU Life Sciences Transition Programme, an effort established between industry and government in July following the June 23 Brexit referendum; its steering group is co-chaired by Neil Mesher, Andrew Witty and Pascal Soriot, the chief executives of Philips Electronics UK and drug giants GlaxoSmithKline and AstraZeneca, respectively. The next meeting with ministers is on Nov. 23.

> "Following the court decision, the Association of British Healthcare Industries said it still had "little clarity as to how negotiations with the EU will proceed, and, indeed, what type of relationship we want."

The government plans to appeal the ruling to the UK Supreme Court. A hearing will take place in December and judgment is expected either by the end of 2016 or in the new year.

Assuming the Supreme Court does not overturn the Nov. 3 judgment, Parliament could, in theory, reject the government's plan to trigger Article 50. Consensus within the UK is that this would be very unlikely to happen, as it would be seen as undermining the result of the June public referendum. A more likely outcome is that members of Parliament demand more information from the government on its negotiating strategy before agreeing to trigger Article 50. That could mean that securing parliamentary approval for triggering Article 50 could be a long process that extends beyond the March deadline.

KEY ISSUES

The life-sciences sector's views on Brexit were recorded in detail in a report that was presented on Sept. 6 to ministers and to the UK EU Life Sciences steering group.

Among other things, the sector is recommending an overarching regulatory cooperation agreement negotiated with the EU in the context of a broader UK/EU special relationship. On the regulatory front, the medtech industry's preferred position is for the UK to maintain continuity with the EU medical devices and IVD regulatory systems, "including full participation in EU regulatory processes and alignment of regulations." More specifically, it is seeking:

- A continued role and active participation in relevant EU committees, with the ability to influence medical technologies policy, guidance and legislation;
- Active participation in device vigilance systems and processes; and
- A medical devices mutual recognition agreement that would include the UK maintaining notified body and competent authority status, continued participation in CE-marking activities related to medical devices, continued ability for UK notified bodies to certify manufacturers and review technical documentation related to medical devices.

In addition, the life-sciences sector as a whole is seeking to secure predictable funding and collaboration for scientific research; access to the best talent; and the ability to trade and move goods and capital across borders.

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'Case For Quality' Aims To Place Greater Device Purchasing Power In Hospitals' Hands

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A report from the Medical Device Innovation Consortium (MDIC) looks to give hospitals greater assurance when purchasing medical devices that the products they're buying are of gold-standard quality.

Under the auspices of "Case for Quality," MDIC's Product Quality Analytics Working Group conducted a pilot program that reviewed publicly available information on knee implants and implantable cardioverter defibrillators. The group is made up of representatives from device manufacturers, health-care providers, US FDA and hospital value-analysis committees.

The goal of the working group was to create "dashboards" of quality and other information on particular products so hospitals could decide on the best types of devices to use to ensure patient safety and satisfaction. The working group discovered that the hospitals found the new quality-related information invaluable as they made purchasing decisions.

> "This is the first step in a long journey of making sure that these hospitals use the right criteria to purchase devices," Dwight Abouhalkah, from J&J and MDIC, says.

"Most hospitals have value-analysis committees or teams that purchase medical devices, and they use certain data to purchase those devices," explained Dwight Abouhalkah, MDIC's program manager for Case for Quality, and director of quality for **Johnson & Johnson**'s medical devices unit.

Abouhalkah explained to *Medtech Insight* that the MDIC working group "set out to test a hypothesis: If hospitals' value-analysis teams actually had access to specific data about product quality outcomes, would that information help those committees make better purchasing decisions? And if they made better purchasing decisions and made the right call, would that improve patient access and outcomes?"

Launched in 2011, the Case for Quality develops best practices, standards, tools and metrics that can be used by both FDA and industry to improve product and manufacturing quality in ways that go beyond compliance with regulatory requirements. FDA's device center teamed with the agency's Office of Regulatory Affairs to create Case for Quality, which is now overseen by MDIC.

When reviewing knee implants and ICDs, the MDIC working group evaluated publicly available information about the products and matched them against seven quality indicators: safety, effectiveness, reliability, patient satisfaction, usability, availability and compatibility.

The public data was collected from several sources, including FDA's Manufacturer and User Device Experience (MAUDE) database, PubMed Central, ClinicalTrials.gov and the ICD registry. Information was also gleaned from data on medical device recalls and chatter about products in health-care user forums.

The data was then analyzed to calculate key performance indicators, which was presented to hospital value-analysis committees via four quality dashboards that contained an overview and rankings by data source, manufacturer and product. The value-analysis committees then provided feedback by way of surveys and focus groups.

"The dashboards show where certain devices fall on the quality spectrum," Abouhalkah said. "After the dashboards were provided to hospital value-analysis committees, the working group basically surveyed the voice of the customer – in this instance, hospitals – to ask, "Is this information that we extracted across these seven quality domains useful to you? And the answer was overwhelmingly 'Yes.'"

MDIC's report offers a litany of recommendations for next steps for the initiative, including conducting a pilot in partnership with a specific registry to improve access to data, working with patient advocacy groups to develop patient-preference metrics, and using enriched data to improve the initial four dashboards.

"By the end of 2017, the goal would be to have a well-documented system for accessing and sharing device quality data," the report states. "If this goal is reached, third-party data analysis teams could use the methods developed to consistently provide accurate information about device quality."

In the meantime, Abouhalkah is aiming to get the word out to hospitals and industry. He discusses the initiative in greater detail in this *Medtech Insight* interview.

Medtech Insight: What should the device industry do with this report, and what should hospitals do with this report? Is the report just basically saying that MDIC needs to do more work on this topic? Or is the report instructing hospitals to look at *this* device or *that* device?

Dwight Abouhalkah: That's a great question. You and I think hospitals have everything down and that they're buying devices based on some huge criteria that they put in some algorithms. But the answer is that they don't. Some hospitals rely on very unscientific methods of trying to buy stuff.

What this report is supposed to do is say, "If we could find information in the public domain that fit these seven domains of what we consider to be quality, would this information be useful to you?" And the answer came back a resounding "Yes, we want this information."

> If this information is useful, now we need further work to make sure this data is reliable, accurate, relevant and spread across the medical device firms accurately."

The report is to inform industry and hospitals that this is information that your customer wants. Let's work with FDA and all the other registries – and maybe a third party – to ensure that the publicly available information in PubMed and ClinicalTrials.gov and other sources is accurate and reliable so when we do these extractions, that hospitals' value-analysis teams will see the value. So, it kind of informs both populations. It informs industry that, "Let's work with FDA and other registries and data sources to make sure information is accurate." And because hospitals say they want this information, then maybe the hospitals and the industry and FDA could work together to make this very seamless and very transparent.

It seems like there's more to come, if you will – maybe another report that would require an additional study.

Abouhalkah: Yes. This is the first step in a long journey of making sure that these hospitals use the right criteria to purchase devices. This is not the end all/be all. It's the first step to say, "Is this information useful when we aggregate it?" If the answer had been "No," then we would probably have been done. But since the answer came back, "Yes, we like this information; we want more of it. How do we get more?" then that's what we'll do.

Again, there are challenges to getting the information. There are biases. We need to work through all of that. So, the report is saying, "Let's work together – FDA, the industry, and these value-analysis teams within hospitals – to make sure this information is accurate, and that when it's aggregated across those seven domains of quality, that the information that you get will help you make a decision to purchase these devices."

How reliable is it to glean quality information from publicly available resources? For example, a lot of Medical Device Reports (MDRs) and adverse events aren't reported by manufacturers, and a lot of recalls aren't reported. How trustworthy can the results be if you're just looking at public information?

Abouhalkah: That's one of the things the working group said, is that there are several significant challenges related to medical device information. Is it unbiased? Is it relevant and is it available? Is it consistently applied? You mentioned MDRs. A lot of firms – or some firms – report everything, and some firms report little. So, if you have one firm that has a hundred MDRs and another firm has three, how reliable and accurate is that? So, part of this pilot is not just to say, "Hey, we've done it; we're good. We're done." Rather, it was to say, "This is a pilot to see what possible challenges there are."

Even though the working group extracted information across the seven quality domains to try and narrow down some of the biases and the challenges, the group realized that we still have challenges. That's the key: If this information is useful, now we need further work to make sure this data is reliable, accurate, relevant and spread across the medical device firms accurately. Because, like I said, some underreport and some report everything. So we went in with these assumptions that it could be biased and that it could have some issues, and we came out saying, "Yeah, it probably does." So further work needs to be done on this publicly available information to make it more accurate and available.

Would this initiative make firms want to offer up information that isn't public that would maybe paint a fuller picture of the quality of its devices? Because they might say, "I'm reporting but my competitor isn't. I want to offer up some additional information ourselves so there's a fuller picture." Because what's publicly available can be skewed.

Abouhalkah: Well, I haven't heard the working group go in that direction. I'm not saying it's not a viable stream. But what I have heard is, for example, the MDR piece – that's actually something they've already looked at and said, "Yeah, there are manufacturers that report one another's MDRs. Maybe this is not something we want to use as a data source. Maybe the information on ClinicalTrials.gov is more important." As for recalls – obviously they either happened or they didn't. So, the working group is looking at the current data sources and asking how reliable they are, and then what can we do as a community to make them more reliable so there is as much transparency as possible.

What about a manufacturer that says, "Look at what they're doing with publicly available data. This and that is what they're looking at. So let's report fewer adverse events or MDRs."

Abouhalkah: I think, in general, people want to report what they believe to fit the regulations and the laws. Because you're asking, "Can people break the law and not report things?" Yeah, they can. But they can do that any time. If firms think, "Well, I'm not going to do X, Y and Z because it might show up on some report two years down the road," well, hopefully that's few-and-far-between, and that those manufacturers are caught and prosecuted.

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Real-World Evidence User-Fee Funding Praised At FDA Meeting

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The nascent National Evaluation System for health Technology was a consistent topic of debate between US FDA and industry during the past year's user-fee negotiations, but eventually made it into a tentative deal that will be presented to Congress for approval. At a Nov. 2 FDA public meeting on the user-fee deal, patient groups said they appreciated FDA and industry supporting the initiative, which initially got pushback from device-makers due to skepticism on how it would benefit companies in the pre-market setting.

FDA, industry, research advocacy and patient advocacy groups discussed how they worked to put a new MDUFA IV deal together during the meeting held at the agency's Silver Spring, Md., headquarters. The research and patient advocacy groups praised FDA and industry for including support for real-world evidence (RWE) data through the NEST system, as well as support for patient-engagement data, in the user-fee agreement.

Eric Gascho, vice president for government affairs at the National Health Council, echoed what other advocacy groups said during the meeting, emphasizing excitement about the use of real-world evidence and patient engagement. While he said they appreciated FDA's previous guidance documents addressing patient preference and collaborations with the Medical Device Innovation Consortium to develop methods for using patient engagement in the regulatory process, they were even more impressed when the issue was included in the user fee deal, with real funds behind it.

"To see this included, to have dedicated funding for [FDA's] patient engagement programs in MDUFA IV, I think is going to be a huge step forward for them to be able to hire, retain and really develop a lot of the staff and expertise in this area," Gascho said.

Photo credit: Ferdous Al-Faruque

MDMA's Mark Leahey at the Nov. 2 MDUFA IV public meeting

On the topic of RWE, he said patient groups were happy to see funding for the NEST program, which they hope will provide a fuller picture of how medical devices perform in clinical use. He added that he'd like to know more about what the NEST steering committee will look like, with the hope that patient advocates will get a sufficient voice to express their concerns and ideas as the program develops.

The draft user-fee commitment letter from FDA notes that no fewer than one representatives each from the four industry trade associations that participated in the MDUFA IV negotiations will be representing on the NEST governing board, making up at least 25% of the board membership. But the letter does not specify what representation from patient groups might be.

Lead FDA negotiator Malcolm Bertoni, director of the Office of Planning in the Office of the Commissioner, pointed to RWE and patient engagement as areas of special interest "that kept coming up" during the year-long negotiations.

"We are very pleased that through this negotiation process, FDA and industry got some commitments and some additional funding through this program to address these issues," he said. "I think this is an important advancement in the overall program."

As previously reported by *Medtech Insight*, the issue of RWE, in particular, had been a sticking point during the negotiations. FDA argued the NEST program would create a new paradigm for following long-term safety and efficacy of products on the market and would allow the agency to approve some devices sooner based on less pre-market data.

Industry however was less convinced that the NEST program warranted user-fee investment, questioning its potential benefit for accelerating pre-market development. But the industry groups eventually agreed to help pay for a pilot of the system through the MDUFA IV timeframe after the agency put up $3m of its own funds to pay for a Coordinating Center, which will be run by the Medical Device Innovation Consortium and tasked with developing the framework for NEST.

Mark Leahey, president of the Medical Device Manufacturers Association, told *Medtech Insight* following the Nov. 2 meeting that industry was on board with FDA's patient-preference initiative from the beginning after seeing it succeed in earlier projects. However, he acknowledged that it took industry time to get behind the RWE initiative.

"Industry maintained from the outset and continued through the MDUFA IV [negotiations] that industry user fees were for the purposes of the pre-market review process, not for post-market activities," he said. "And as the discussions continued, FDA was able to make the case that these investments would accelerate the clinical trial process, would allow for label expansions based on real-world evidence; they had a nexus toward pre-market efficiencies."

But, Leahey cautioned, industry is taking a "trust but verify" approach toward RWE by providing a significant amount

of resources ($30m) while keeping an eye on how it turns out. Included in FDA's commitment letter is a provision for an independent assessment of NEST to determine whether the benefits FDA talks about are realized. Based on the outcomes of the assessment, industry will figure out how to potentially fund NEST beyond MDUFA IV, Leahey said.

"If they achieve their objectives, I can see industry continuing to provide some support, but it was indicated by many folks here, as well, [that] there was an interest in providing congressional appropriations," he added.

The NEST program is set up as a pilot program that, according to FDA's commitment letter, will initially focus on two medical device product codes, one PMA and one 510(k) product type. If successful, it would be scaled up.

> "RWE and patient engagement were areas of special interest "that kept coming up" during the year-long user-fee negotiations, FDA's Malcolm Bertoni says.

Leahey did not comment on what specific products might be good candidates for the NEST pilot, but did note that for other products that have registries already in place, researchers have been able to leverage data from them successfully. For the pilot, he says he would like to see information on products that are not already reaping the rewards from registries and could benefit more from RWE.

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Bill Hawkins Appointed Chair At Tricuspid Valve Startup 4Tech

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Former **Medtronic PLC** chair and CEO Bill Hawkins has been elected chairman of **4Tech Inc.**, a clinical-stage startup firm that developed the *TriCinch* transcatheter tricuspid valve repair device.

The appointment was announced Oct. 28. As the first chairman of 4Tech, Hawkins will help with the clinical validation and subsequent commercial launch of the *TriCinch TTVR* device. 4Tech announced last month that the device was used in the first-ever transcatheter valve repair that did not use of transesophageal echocardiography or general anesthesia to treat patients suffering from tricuspid regurgitation.

Hawkins is currently also a trustee of **Duke University**, vice chair of **Duke University Health System**, chairman of **Bioventus Inc.**, lead director at **Immucor Inc.** and director of **Halyard Health Inc.** He also previously served on the board of AdvaMed and was a chairman of the Medical Device Innovation Consortium, the first-ever public-private partnership between industry and FDA.

"Bill has enormous credibility and tremendous experience in the medical device industry. I personally look forward to his participation as we continue to establish TriCinch as a … reproducible percutaneous solution to restore tricuspid regurgitation," said Carine Schorochoff, 4Tech CEO.

William Hawkins, chairman, 4Tech Inc.

Tricuspid regurgitation affects more than three million patients in the US and Europe, making the potential TRI patient population approximately two-thirds the size of the large mitral regurgitation population.

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VC DEALS ANALYSIS:

Little Hope Of Recovery As October Plummets

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Those who had gambled on 2016 being a bumper year for venture investment may have to brace themselves for a lost bet.

The boost in September's venture financing activity following a long summer lull looks to have been a blip, rather than the start of an upward as October recorded the lowest venture deal volume and deal value this year to date. Last month, *Medtech Insight*'s VC deal tracker recorded 14 transactions that raised $1m or more, representing over a third fewer than the 22 deals seen in September and almost half of the 27 deals recorded in October 2015.

The total amount raised from the 13 deals that disclosed financial details was a paltry $240m, which is lower than any other month in 2016 and any other Octobers since 2013. (see Figure 1)

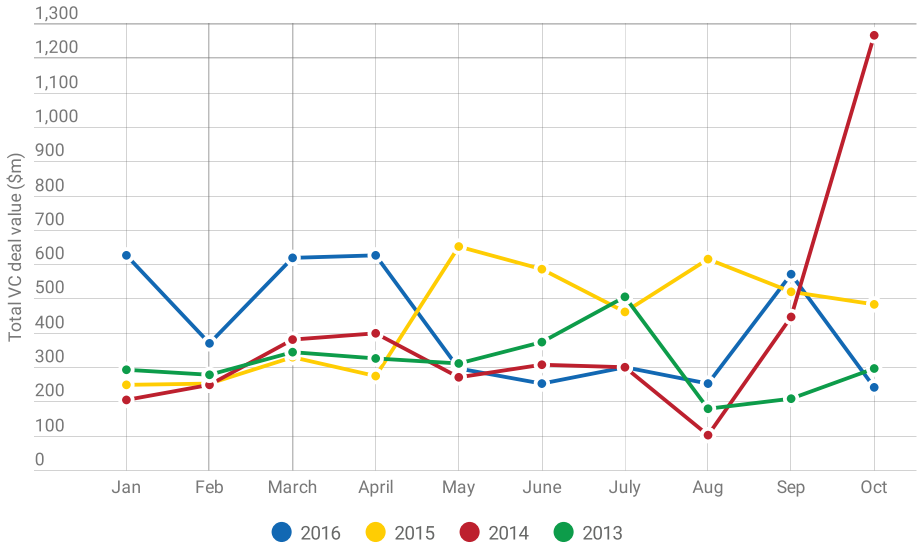
The weak performance not only reflects the overall low deal volume but also the paucity of large-sized deals above $40m. It is worth noting that October did have a relatively large number of deals in the mid-sized $30m-$40m – four compared to three in September and two in October 2015 – and that half of these were sizeable series A rounds. However, September and October last year benefited from deals above $40m and both months also bagged a nine-figure deal, with September seeing a $215m round raised by drug delivery company Intarcia Therapeutics and October 2015 recording a $115m round by gene testing company 23andme. (see Figure 2).

With October's modest contribution to the annual tally, 2016 has so far raised around $4.15bn in venture funds, putting this year over $1bn behind 2015's full-year total of $5.23bn. Chances of recovering that significant shortfall looks very unlikely, unless the last two months see a couple of major nine-figure fundraisings that could at least put 2016's total on par with that of the previous year.

CLICK
For more details about VC deals, go to Medtech Insight's VC deal tracker: https://medtech.pharmamedtechbi.com/datasets/vc-funding

FIGURE 1

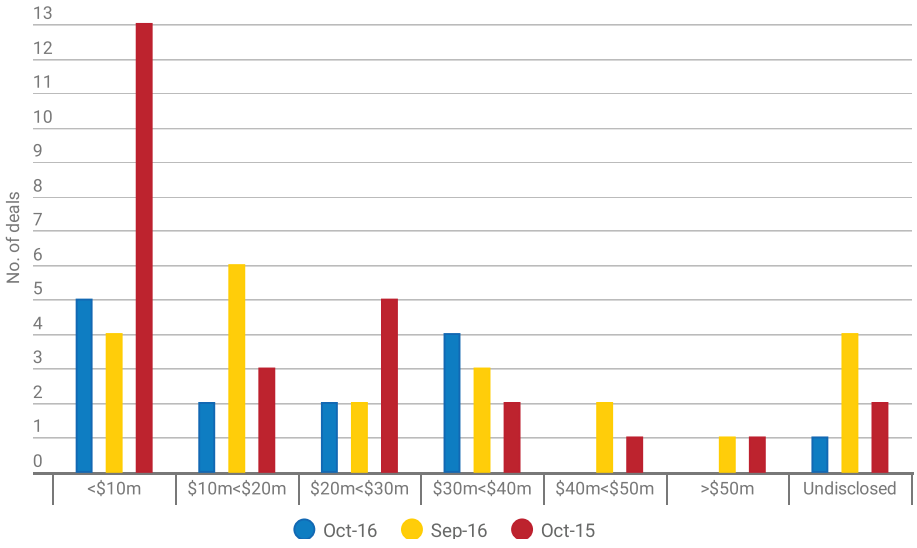
Total amount raised by month, Jan.-Oct., 2013-2016



Source: Medtech Insight

FIGURE 2

No. of deals by amount invested



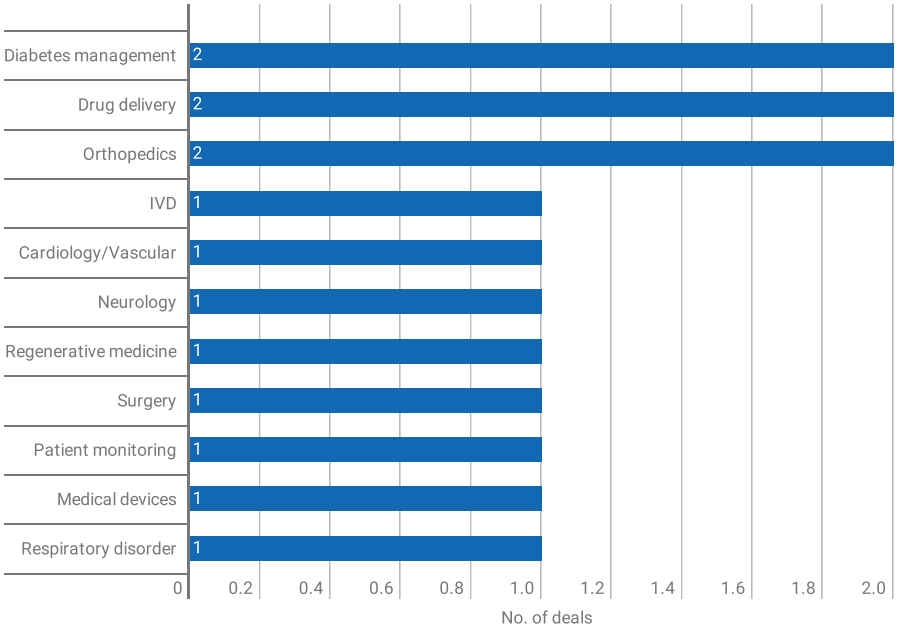
Source: Medtech Insight

ORTHO, DIABETES, DRUG DELIVERY

Venture investments were spread evenly across a range of technologies addressing different sectors, although companies in

FIGURE 3

No. of deals by product/therapy sector, October 2016



Source: Medtech Insight

orthopedics, diabetes management and drug delivery each recorded one more deal than the others. (see Figure 3)

The two ortho deals also made up the two biggest rounds in October. (see Figure 4) Swedish company **BoneSupport AB**, which specializes in injectable, osteoconductive bioceramic bone fillers, raised $37m to advance commercialization of its antibiotic-eluting products *Cerament G* and *Cerament V*, and Relievant Medsystems raised $36m to accelerate sales and marketing of its *Intracept* intraosseous nerve ablation system, which was recently cleared by the

Orthopedics is currently the third most popular sector for investment, with 14 deals in total this year to date. If it continues to pull in the investors for the remainder of the year, it looks likely to retain its position and push surgery – last year's number three most popular investment space – down to fourth place.

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FIGURE 4

Top 5 medtech VC deals by amount raised, October 2016

RANKING	COMPANY	BASED IN	PRODUCT/ THERAPY SECTOR	AMOUNT RAISED	FINANCING ROUND	TOTAL INVESTMENT
1	Bonesupport	Lund, Sweden	Orthopedics	$37m	Undisclosed (includes debt financing)	$107m
2	Relievant Medsystems	CA, US	Orthopedics	$36m	Undisclosed	Undisclosed
3	Bigfoot Biomedical	CA, US	Diabetes management	$35.5m	Series A	Undisclosed
4	Enable Injections	CI, US	Drug delivery	$30m	Series A	Undisclosed
4	Veritas Genetics	MA, US	IVD	$30m	Series B	$42m

M&A ANALYSIS:

October Deal Volume Takes A Nosedive

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The surge of medtech M&A deals in September failed to keep the momentum going in October, with a sharp drop in deal volume, dashing hopes of a Q4 turnaround. *Medtech Insight*'s M&A deal tracker recorded ten mergers and acquisitions that were announced and/or completed, marking October as one of the weakest months of the year so far.

Deal volume plummeted from the September boom, which recorded 23 deals, and was not even able to surpass August's modest 13 deals. October's performance was also a considerable decline from the 17 deals recorded in the same month 2015. (see Figure 1).

In terms of deal spread by product/therapy sector, IVD continued to lead the way with four deals, and one deal each in neurology, digital health, regenerative medicine, cardiology and drug delivery.

Out of the ten deals recorded this month, only two deals disclosed the financial terms. UK diagnostics company **Oxford Immunotec Global PLC** acquired US company **Immunetics Inc.** for $12m deal, while on the other end of the scale, there was **Pfizer Inc.**'s agreement to offload its infusion therapy business, **Hospira Infusion Systems,** to **ICU Medical Inc.** for a $1bn cash and stock deal.

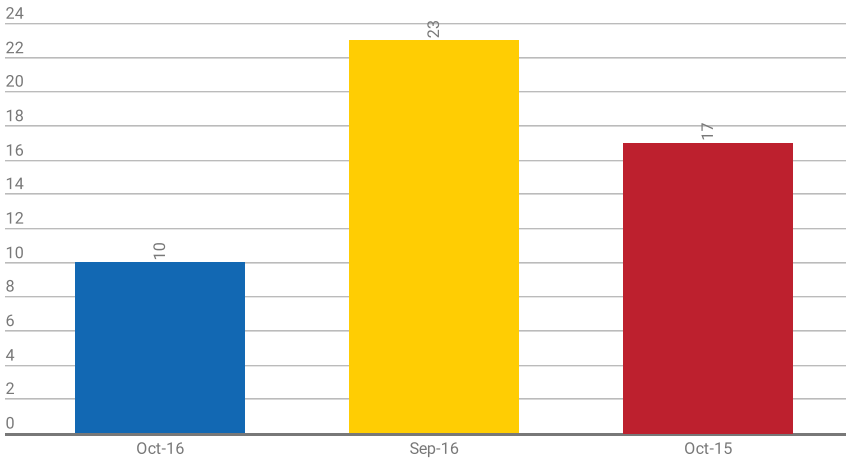
This is the biggest deal of the month and will give Pfizer approximately $400m in newly issued shares of ICU Medical stock and $600m in cash from ICU Medical. The cash element of the consideration is split between $90m in working capital and $510m cash from ICU Medical. Under the terms of the agreement, Pfizer also have the right to nominate one director to the company's board.

Pfizer acquired Hospira Infusion Systems as part of its $16bn acquisition of **Hospira Inc.** in 2015. The divestment to ICU is expected to complete in the first quarter of 2017 and will result in Pfizer owning approximately 16.6% of ICU Medical.

ICU Medical said the combined businesses would create a "leading pure-play infusion therapy company" to compete in the US market and would extend its global reach with direct operations in over 20 countries.

FIGURE 1

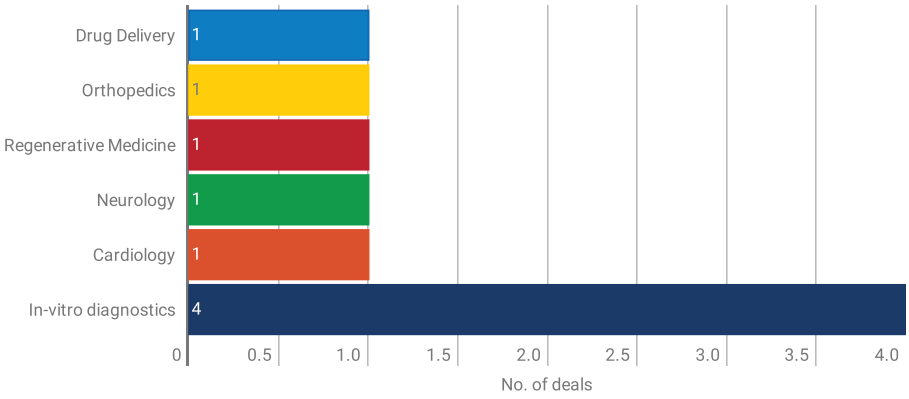
No. of M&A deals, Oct. 2016 vs Sept. 2016 vs Oct. 2015



Source: Medtech Insight

FIGURE 2

M&A deals by product sector, October 2016



Source: Medtech Insight

OTHER NOTEWORTHY M&A DEALS

In October, Danaher increased its portfolio of life science businesses with the acquisition of chromatography solutions business **Phenomenex**. The privately held company has over 7000 chromatography products for application in clinical research, industry, government and academic laboratories. The deal will further extend Danaher's presence in the life sciences space with its portfolio including **SCIEX, Beckman Coulter Life Sciences, Pall, Leica Microsystems and Molecular**

Devices. Phenomenex have confirmed they will operate as a standalone company and retain the Phenomenex brand, its personnel and site locations.

One deal that marks the move toward digitalization of healthcare comes from **BBISolutions OEM Ltd**, a contract provider of lateral flow diagnostics and biological raw materials. BBI acquired the remaining share of a joint venture it had set up with **Novarum DX Ltd**. The mobile technology company develops smart phone applications that allow users to read and share results of diagnostics tests.

Healthcare private equity firm Shore Capital Partners got its return on investment when it closed a deal to sell one its portfolio companies, laboratory diagnostics service provider ClearPath Diagnostics, to **Laboratory Corp. of America Holdings**. Founded in 2002 in New York, ClearPath provides pathology outreach services in a number of US states and was under the management of Shore Capital as it expanded services into more states. LabCorp said the acquisition would combine the company's women's health services with ClearPath's local outreach services to form "an unmatched blend of value and quality" to their obstetric and gynecologic customers and patients.

In 2016 so far, there have been 154 M&A deals. With 2015 having recorded 237 deals in total, the next two months would need to see over 80 new deals come through to match last year's M&A volume – a very unlikely achievement.

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Acarix's CADScor Attracts Chinese Investment

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Riding on the growing wave of Chinese investor interest in foreign companies, Scandinavian IVD firm **Acarix** has landed investment in the million-dollar range (or "double-digit million" in Swedish Krona) from Puhua Jingxin Guzhou Health Management Partnership to accelerate the commercial launch of its CE-marked *CADScor* system. CEO of Acarix, Søren Rysholt Christiansen told *Medtech Insight* the deal was not just a financial investment but was formed with the intention to set up a joint venture in China (Acarix China) to deal with regulatory registration, marketing and sales.

Acarix's CADScor was developed for diagnosing patients suspected of coronary artery disease (CAD) based on the detection of diastolic murmurs from coronary turbulence. The technology uses acoustic signals with advanced algorithms to identify obstructed blood vessels. The device – which consists of a disposable adhesive patch and sensor with microphones and a touch display – is attached to a patient's body and provides a patient-specific CAD-score in under 10 minutes. The technology is designed to be non-invasive, convenient and cheaper than conventional techniques for CAD detection, like CT angiography.

Acarix was spun out of Aalborg University in Denmark in 2005 and received CE-marking for the device in August 2015. Since the approval, the company has focused on refining CADScor's algorithm based on clinical data obtained from the Dan-NICAD study and presented the device at a number of conferences. Christiansen said the Chinese cash injection would help "ramp up production and sales organization" ahead of its planned launch of CADScor in Q2 of 2017. The company will initially focus commercialization on Germany, UK, Sweden and Denmark.

Acarix currently holds a nominal share capital of 19.4 million shares, with investors Sunstone Capital, Seed Capital and Coloplast A/S holding more than 10% of shares. The company received DKK6.8m ($1m) in funding from the Danish National Advanced Technology Foundation between 2007-2011 and DKK5.3m between 2011-2014 from the Danish Business Innovation Fund. To date, it has raised DKK66.6m in venture capital and SEK 120M in investment.

Puhua Jingxin is a joint healthcare fund aligning strategic resources from Puhua Healthcare and major pharmaceutical company Zhejiang Jingxin Pharmaceuticals. Jingxin has previously invested in a medical device company in Israel and a US pharmaceutical company.

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Acarix's CadScorSystem

Photo credit: Acarix

Acarix received CE-marking for CadScor in 2015.

Medtronic Issues UK Warning On Implantable Pump Safety

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Two patient deaths have been tied to the use of an implantable infusion pump that has already been mostly withdrawn from the US market over quality issues, **Medtronic PLC** revealed in a letter to UK physicians concerning its *SynchroMed II* implantable infusion pump.

The October field safety notice states that SynchroMed II pumps have a potential for over-infusion, meaning patients might get more medication than required. While an alarm on the pump should sound when it is out of medication, it may not if the medication flows too quickly, Medtronic says.

The safety notice reports 103 adverse events through July 5, 2016. These include five incidents of over-infusion, two of which led to patient deaths. Around 238,000 of the pumps have been implanted since the device hit the market.

The problems have no single cause, Medtronic says. Instead, over-infusion is tied to several factors, including normal variation in pump components and the manufacturing process, as well as clinical-use factors such as use of non-indicated drug formulations, overfilling of the pump reservoir, operating the pump with no fluid in the reservoir, catheter occlusion, and pump stops or motor stalls lasting more than 48 hours, the safety alert states. But while multiple factors appear to be at play, the safety alert also states that the pump was being used with a non-indicated drug at the time of the incident in 99 of the 103 adverse events.

The company isn't recalling the device in the UK or encouraging users to replace the pumps, the safety notice states.

In April 2015, Medtronic signed a consent decree with the US government promising not to make or distribute the implantable infusion pumps, except in limited circumstances, until the company corrected quality system violations identified by the agency. The consent decree followed warning letters issued to **Medtronic Neuromodulation** plants in 2006, 2007 and 2012, as well as multiple recalls. Like the most recent UK safety alert, the US action did not require the recall of pumps currently in use.

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Boston Scientific Stops Roll-Out Of Lotus Edge TAVR To Resolve Locking Problem

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Boston Scientific Corp. announced it is voluntarily removing field inventory of the *Lotus Edge* repositionable transcatheter aortic valve system, just weeks after launching it at select few European sites, after receiving reports that some of the devices could not be locked after deployment.

If the valve cannot be locked once it is in place in the aortic annulus, the procedure cannot be completed with that valve. So far, in all reported instances of the locking malfunction with Lotus Edge, the interventionalists were able to retrieve the malfunctioning valve and successfully implant a new valve replacement. So far, the issue has been reported in seven out of about 200 patients implanted with Lotus Edge.

This field action will not impact patients who have already been implanted with the device, the company says.

"The company is completing an evaluation to identify the root cause of the issue," Boston Scientific said in a prepared statement Nov. 2. "Physicians are advised to use the previous-generation *Lotus* valve system, which continues to be available in Europe."

Boston Scientific announced the CE mark of Lotus Edge on Sept. 19. The company expects it to be more competitive with devices from **Medtronic PLC** and **Edwards Lifesciences Corp.** compared to the original version of Lotus because the newer device is more flexible and includes a narrower delivery catheter. The company is also sponsoring the REPRISE IV trial comparing Lotus Edge to Edward's *Sapien 3* in intermediate risk patients and the REPRISE V trial, which will compare Lotus Edge to surgical valve repair in patients considered to be at low risk during surgery.

The company is confident this delay will not prevent Lotus Edge from taking market share in Europe, according to Wells Fargo analyst Larry Biegelsen, who spoke to Boston Scientific leaders at the Transcatheter Cardiovascular Therapeutics (TCT) meeting in Washington, DC.

"No timing was provided for when the valve will return to market, but management does not believe any valve re-design will be required," Biegelsen wrote in an Oct. 31 research note. "Management said its decision to take Lotus Edge off the OUS market will not result in any change to 2016 guidance or US commercialization timing." The company expects US FDA to approve the original Lotus in late-2017 based the results of the 1,032-patient REPRISE III IDE study.

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TCT ROUND-UP:

The Next Generation Of Drug-Eluting Stents, Drug-Coated Balloon Featured At Washington Conference

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One of the world's largest showcases for new interventional cardiology technology, the 2016 Transcatheter Cardiovascular Therapeutics (TCT) 2016 scientific sessions, were held Oct. 29-Nov. 2 in Washington, DC. This year's edition of TCT featured many presentations on new drug-eluting coronary stent technologies, as well as drug-coated balloons for peripheral interventions.

CLICK
For more of our coverage of TCT 2016, go to http://bit.ly/29zivFF

Boston Scientific's Synergy Matches Durable Polymer DES In TRANSFORM-OCT

Results of the TRANFORM-OCT trial, announced at the Transcatheter Cardiovascular Therapeutics meeting, show a high rate of strut coverage and low rates of neoatherosclerosis with **Boston Scientific Corp.**'s *Synergy* everolimus-eluting coronary stent with a biodegradable polymer.

"TRANSFORM-OCT adds a novel mechanistic dimension to the assessment of new-generation drug-eluting stents, consolidating the understanding that well designed and biocompatible polymers, regardless of whether they are durable or biodegradable, may favorably impact the long-term vascular response of these stents," explained principal investigator Giulio Guagliumi of the Ospedale Giovanni XXIII in Bergamo, Italy, who promoted and implemented the trial with an unrestricted financial support from Boston Scientific**.**

TRANSFORM-OCT randomized 90 patients with multivessel disease coronary disease to treatment with Synergy or **Medtronic PLC**'s *Resolute Integrity* zotarolimus-eluting stent. The first co-primary endpoint was maximum length of consecutive frames with uncovered struts after three months as shown by optical coherence tomography (OCT), powered to show the non-inferiority of Synergy. The other co-primary endpoint was the percentage of patients presenting with frames of neoatherosclerosis on OCT imaging at the 18-month follow-up, powered to show the superiority of synergy.

At three months, the median percentage of covered struts was 79.1% in the Synergy group and 78.4% for the Resolute Integrity group, showing the non-inferiority of Synergy, and at the 18-month follow-up, the median percentage of covered struts was 99.4% in the Synergy group and 98.0% in the Resolute Integrity group. In-stent neoatherosclerosis at 18 months 11.6 % in the Synergy group and 15.9% in Resolute Integrity group, which is statistically similar, but the average number of OCT imaging frames with neoatherosclerosis was a very low in both groups – 1.1 for in Synergy and 2.5 in the Resolute Integrity group.

Boston Scientific is betting that metal stents with bioabsorbable polymers will win out over completely bioabsorbable stents because histological evidence shows the polymer on drug-eluting is often what prevents the vessel wall from healing, rather than the metal stent itself, and metal is a much better material than polymer for making strong stents with thin struts.

This hypothesis may have received some support earlier at TCT when the results of the ABSORB II trial of **Abbott Laboratories Inc.**'s *Absorb GT1* everolimus-eluting fully biodegradable stent improved vasomotor reactivity or late-lumen loss compared to Abbott's *Xience* metallic everolimus-eluting stent.

OCT Data Looks Good For Amaranth's Bioasbsorbable Stents

Nine-month clinical and imaging results from 62 patients treated with **Amaranth Medical Inc.'**s *Fortitude* sirolimus-eluting bioresorbable scaffold, presented at the TCT conference on Oct. 31, show promise for the company's thin-strut biodegradable stent technology.

The results of the FORTITUDE single-arm trial, presented by Antonio Colombo from the Ospedale San Raffaele in Milan, showed the average minimum lumen diameter coronary segments stented with Fortitude was 2.4mm nine months after the procedure. The average late lumen loss in these segments was 0.17mm, as measured with quantitative angiography. During the nine-month follow-up period, there were three cases of target vessel failure, one patient died of a non-cardiac cause, two patients suffered a myocardial infarction related to the stented vessel, and one patient needed a target lesion revascularization due to ischemia, but there was no evidence of stent thrombosis.

Also optical coherence tomography analysis found only one case of scaffold discontinuity within healthy neointimal, which is "very encouraging and supports not only the biomechanical

stability of the device but also confirms the potential for future miniaturization of the strut thickness," explained co-principal investigator Juan Granada of the Cardiovascular Research Foundation Skirball Center for Innovation in New York.

Amaranth CEO Kamal Ramzipoor told *Medtech Insight* that the struts of Fortitude are 150 microns thick, which is about the same thickness as Abbott's Absorb GT1, but Amaranth's technology has a "significant advantage" over Abbott's because Fortitude has the ability to over-expand, whereas Absorb has very limited capacity for over-expansion, and has much greater radial strength than Absorb, according to Ramzipoor. "We want [the bioabsorbable stent] to perform very close to the metallic stents, which do have the over-expansion capacity," he said. "The stent doesn't always match the size of the artery, so some fine-tuning of the dimensions has to take place. The over-expansion capacity gives that latitude to the physician to fine-tune the final diameter of the scaffold to the size of the artery to prevent things like late thrombosis."

Despite the encouraging clinical trial results, Amaranth is not planning to commercialize Fortitude. Instead, it is focusing on developing the next generation of its bioabsorbable sirolimus-eluting stent made of the same proprietary high-molecular weight polylactide material called. This stent, called *Aptitude* has 115 micron thick struts and early clinical experience with Aptitude confirms its thin stent struts allow it to be delivered into complex anatomies while retaining a high radial strength, according to Amaranth.

Aptitude is being tested in the RENASCENT II trial, which competed enrollment of 60 patients in May. The company says that the patients in RENASCENT II who have reached the nine-month imaging follow-up show comparable clinical results and mechanical stability as patients treated with Fortitude in clinical trials. Amaranth expects to start a CE Mark for Aptitude this quarter and earn the CE Mark by the end of 2017.

Also, on Nov. 1, Amaranth announced the start of RENASCENT III, a 70-patient single-arm trial of this third-generation stent, called *Magnitude,* which has stent struts less than 100 microns thick.

Final ILLUMENATE Results Set-up Spectranetics' DCB For Late 2017 US Launch

Spectranetics Corp.'s *Stellarex* paclitaxel-coated balloon catheter performed about as well in the ILLUMENATE US pivotal trial as it had in previous clinical trials, giving the company confidence FDA will approve it in time for a US launch in the second half of 2017.

Final one year results from 300 patients in the US ILLUMENATE trial were presented Nov. 2 at the TCT conference by Sean Lyden of the Cleveland Clinic in Ohio.

Patients in the trial all had symptomatic leg ischemia, requiring treatment of the superficial femoral artery or popliteal artery and were randomized to treatment with Stellarex or a regular non-drug coated peripheral balloon catheter. Lyden said the US trial represents the most complex patient population ever addressed in drug-coated balloon IDE trial. The co-morbidities for patients in the group randomized to Stellarex included high rates of severe calcification (43.9%), diabetes (49.5%), renal insufficiency (18.0%) and cardiovascular disease (45.0%).

After one year, the primary patency rate was 82.3% for the Stellarex group and 70.9% for the control group and freedom from clinically driven target lesion revascularization was 93.6% for the Stellarex group and 87.3% for the control group, meeting both primary endpoints for the trial.

Despite the difficult patient population, the outcomes in the US trial are similar to that of other ILLUMENATE trials of Stellarex. Interim one-year data from 220 patients in the ILLUMENATE global study, released in June, showed that superficial femoral and popliteal arteries treated with Stellarex had a 93.9% freedom from clinically driven target lesion revascularization rate and a primary patency rate of 86.5% after one year. In the ILLUMENATE European trial, Stellarex produced a 12-month patency rate of 89.0%, versus 65.0% in the control arm, according to Spectranetics.

Spectranetics says the proprietary *Enduracoat* coating technology allows the balloon's surface to maintain high-coating stability with minimal drug-loss, which allows the paclitaxel delivered by the balloon to stay in the vessel wall longer to prevent neointimal hyperplasia. Co-primary investigator Prakash Krishnan of Mount Sinai in New York said: "First-generation drug-coated balloons forced us to make a choice between top-tier clinical outcomes and the potential safety advantages of a lower drug dose. Based on the compelling Stellarex DCB study results, we no longer need to compromise."

Stellarex has been available in Europe since January 2015, and the company said it has submitted the US pivotal data to FDA and expects to launch it in Europe in the second half of 2017. At TCT, Spectranetics CEO Scott Drake said, "If you see this 82 percent patency in a relatively complex lesion set – it's kind of stent-like results without leaving an implant behind. I think that's a big step forward for patient care and a very important tool for customers."

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CONTINUED FROM PAGE 1

SHIFTING THE TONGUE WITH NEUROMODULATION: INSPIRE MEDICAL AND NYXOAH

Neuromodulation is one approach that some companies have taken with their OSA treatment technology. The hypoglossal nerve controls almost all tongue muscles, and neuromodulation devices for OSA stimulate this nerve in order to move the tongue out of the airway during sleep.

Inspire Medical Systems Inc.'s fully implanted neuromodulation system earned US FDA approval in April 2014 for use in certain moderate to severe OSA patients who cannot tolerate CPAP. An implanted battery connects to a breathing sensor and stimulation lead that delivers mild electrical pulses to the hypoglossal nerve in sync with the patient's breathing. The system is turned on and off by an external remote. Its most recent iteration, which became available in July this year, offers data tracking features.

Led by **Medtronic PLC** veteran Tim Herbert, Inspire was spun off from Medtronic in 2007 and raised $80m before FDA approval. Investors include **OrbiMed**, the **Johnson & Johnson Development Corporation**, **Aperture Venture Partners**, **Kleiner Perkins Caufield Byers**, **US Venture Partners**, **Synergy Life Science Partners**, Medtronic, **GDN Holdings** and **TGap Ventures**.

Inspire is growing rapidly, moving from $3.8m in revenue in 2014 to $8m in 2015 and is expected to exceed $15m in 2016. In August, the company marked its 1,000th implant.

After 18 months of use, *Inspire therapy*'s subjective and objective treatment effects remained consistent with the 12-month results without the need for additional programming, as published in the October 2015 issue of *Sleep*. According to a follow-up published last January in *Otolaryngology-Head and Neck Surgery*, 81% of 116 patients were using Inspire seven days a week after 36 months. Additionally, of 98 patients who underwent sleep testing at the three-year mark, 74% showed a successful degree of reduction in the standard outcome measure, the apnea-hypopnea index, going from a baseline of 28.2 apneic events per hour to just 6.2 three years later. Five-year data should be available in the middle of 2017, Herbert says, and a next-generation system will be released next year as well.

Inspire earned NUB 1 status in Germany this year, meaning the government will fund the devices. This will make it easier to open more centers and train more otolaryngologists and neurosurgeons in its implantation.

The company, now over 80-employees strong, is focused on arranging reimbursement with Medicare and private insurance companies, of which over 130 have approved Inspire on a case-by-case basis. Inspire is also approved for reimbursement through the VA and at military hospitals. After raising a final round of capital to fund that effort, Herbert says the plan is an initial public offering.

The Belgian company **Nyxoah** 's implantable neurostimulation system for the hypoglossal nerve leaves battery and most electronics outside the body, eliminating the risks associated with tunneled electrodes and implanted battery pack in the chest, such as pocket infection or long-term lead failure. Rémi Renard, vice-president of therapy development, a biomedical engineer with 10 years' experience in cardiac rhythm management (CRM) at St. Jude Medical and Boston Scientific, says Nyxoah's will be the only lead-and battery-free implantable system available on the market. Since September, the company has been helmed by Enrique Vega, a senior executive in the cardiac rhythm management, sleep apnea, and neurostimulation fields, who replaces co-founder Robert Taub as CEO.

The *Genio Implantable Stimulator* contains an antenna and bilateral stimulation electrodes. It is sutured, saddle-like, to the genioglossus muscle of the tongue through a minimally invasive surgical procedure, its electrodes contacting both left and right branches of the hypoglossal nerve. At bedtime, the patient attaches a disposable patch under the chin. This patch holds the activation chip, which includes a battery and chipset. The chip delivers a radiofrequency signal that crosses the skin to the implant, which converts the RF energy to current that is delivered to the nerve through the electrodes. This stimulation leads to the contraction of muscle fibers in the tongue, causing motion that opens the airway. Upon waking, the patient discards the patch and plugs in the activation chip for recharging. Renard says bilateral stimulation, unique to Nyxoah, may offer more efficient treatment, and notes that the device will be proven MR- conditional and compatible in patients who already have a pacemaker or implantable cardioverter defibrillator. Further, the activation chip is open-platform, allowing for technical enhancements years after implantation.

The Inspire Therapy

US FDA-approved neuromodulation device for OSA

Nyxoah's Genio Implantable Stimulator

The device will be the only lead- and battery-free implantable neuromodulation system for OSA.

Apicure's Winx

The system provides light negative pressure to move the tongue and soft palate out of the airway.

"We do not position Nyxoah as a competitor to the CPAP market," Renard says. Rather, he says, the company will position itself as second-line therapy for those moderate to severe OSA patients who have failed or refused CPAP therapy. That pool, according to company estimates, amounts to 400,000 people annually in the US and an equal number in Western Europe.

With 28 employees, mostly in R&D, Nyxoah was cofounded and angel-funded in part by experienced pharma entrepreneur Robert Taub in 2009. Now chairman of Nyxoah's board, Taub also founded and managed Omrix Biopharmaceuticals throughout a NASDAQ IPO. The company was acquired by Johnson & Johnson in 2008 for $438m. Nyxoah's initial R&D was done in part in collaboration with Germany's Fraunhofer research institute. Today, most R&D activities are directly managed internally. Nyxoah has submitted more than 100 patent applications around the world, with 30 patents granted in the US to date.

On July 7, Nyxoah announced the completion of a $20m fundraising round, led by Dutch venture firm **Gilde Healthcare**. The round will fund its planned CE mark trial, BLAST OSA, a non-randomized multicenter study slated to begin in H1 2017, and a subsequent US IDE study. The company declined to comment on previous funding rounds.

While Renard doesn't see CPAP going away any time soon, he believes Nyxoah's device will become second-line treatment for moderate to severe OSA patients who decline or are noncompliant with CPAP, and, perhaps, first-line for selected patients based on a better understanding of their phenotype. Future research will include exploring a possible expansion of indications into patients with higher BMIs, as well as whether their implanted system might have diagnostic applications.

"The growth of CPAP therapy is going to slow down, but alternative treatments such as neurostimulators are going to gain space in the OSA field--that's for sure," Renard says.

LIGHT SUCTION: APNICURE

ApniCure was co-founded in December 2007 by engineer and medical device veteran Matt Vaska, who invented its technology after talking with his father, an OSA sufferer who disliked CPAP. Vaska thought of using negative pressure to pull the tongue and soft palate out of the airway. He built a prototype out of a hockey mouthguard, then tried it on himself, demonstrating with CT images that the airway indeed opened when light suction was applied.

Sleep physicians liked what they saw, and Vaska soon garnered $2M in angel funding from Headwaters Capital Partners. Medical device veterans Jed Crowe, Jonathan Podmore, and Chris Daniel were cofounders. Shortly thereafter, in early 2008, US Venture Partners came in at $2m. A series B in 2009 raised $13m led by **Kleiner Perkins Caufield Byers**; a series C in 2010 raised $38m led by **Capricorn Investment Group**, and a $16m round closed in March 2016 from **US Venture Partners**, **Capricorn**, and Headwaters Capital Partners.

Using the nonsignificant risk IDE pathway, the Apnicure team refined Vaska's prototype in iterative clinical studies approved by local IRBs, without the need for animal studies. A multi-site national FDA trial of the Winx device in 2010-2011 earned FDA 510(k) clearance in 2012.

Winx works by providing a light negative pressure—equivalent to drinking water through a 20-inch straw—in the mouth via a mouthpiece, which moves the tongue and soft palate forward and out of the airway. A tube connects the mouthpiece to a small unit at the bedside. Winx does not move the jaw forward, as do mandibular repositioning devices for OSA. Patients then breathe through the nose during sleep. The device is quiet and small enough to pack easily for travel. The company holds 16 US patents, with more pending in the US and abroad.

John Stevens, MD, a cardiac surgeon and entrepreneur with Headwaters Capi-

tal Partners, says the device feels like a cross between a hockey mouthguard and an Invisalign device. "For people who refuse to use CPAP--at least 10-12 million Americans--I think this is a really attractive solution for them," Stevens says. "I think it'll be attractive for the bed partners of those people with sleep apnea, too."

The company now has under 20 employees. Initially, its strategy was to market Winx through sleep labs—but ApniCure soon found that their target patient population of CPAP non-compliers aren't to be found at sleep labs (they tend not to return once they give up on CPAP).

Instead, the company developed a direct-to-consumer model. Patients find the company online, via Facebook or Google. They are referred to telemedicine providers, who can determine whether the product is right for them. The patient then pays $1,595 for Winx—with the mouthpiece component sized to fit the patient's mouth via a bite wax kit received through the mail. Payment plans are available, and the company provides a sixty-day money-back guarantee.

The use of telemedicine services for sleep medicine was endorsed by the American Academy of Sleep Medicine last year.

"The obstacle in the current paradigm is that physical sleep labs [constitute] 80% of revenue generated by sleep docs," Stevens notes. "[Telemedicine physicians] don't have an incentive to do sleep testing…So the economic incentives are aligned with doing what's right for the patient."

Patients love Winx, Vaska says. "It's all done by mail, Internet, and phone, which is working fantastically well for us," Vaska says. "We've had to turn our internet marketing down because we can't handle the volume." Currently the company is working to build enough infrastructure to fulfill orders in California. They expect to go national in 2017.

"The typical medtech [marketing] model is a lot more expensive—you have to hire sales reps, they're trying to run around to get to every sleep lab in the country," Vaska adds. "Here, it's all inside sales, a call center plus internet. It's a much more cost-effective model….What I was surprised by was how effective particularly digital marketing is and how easy it is and how much data you get from it. For consumer medical, it fits fantastically well."

Photo credit: Airing

The technology uses microblowers and works like a micro CPAP device

Vaska earned his chops at **Heartport Inc.**, **Stryker Endoscopy**, and **Raychem**, then founded **Epicor Medical Inc.**, selling its novel cardiac ablation system to St. Jude Medical in 2004 for $185m. Possible future directions for ApniCure include R&D into the snoring market as well as the in-hospital airway maintenance market.

CROWDFUNDED MICROBLOWERS: AIRING

Burlington, Mass.-based **Airing** made headlines in June 2015 when it launched a crowdfunding campaign for its micro-CPAP device. As of this fall, over 17,000 backers have raised more than $1.6m, and the company has gained heavy press coverage in part for its unusual fundraising approach.

Company president Stephen Marsh developed the *Airing* device, which is designed to weigh under an ounce and fit into the nostrils with soft silicone buds. Its electrostatic micro-blowers—hundreds operating in parallel—are designed to generate a range of pressures up to and in excess of 20cm of water, a typical maximum pressure used in conventional CPAP. Marsh developed the blowers under the auspices of Airing's parent company, **Encite LLC**, which was founded in 2006—the blowers were originally meant to cool computer chips. With an anticipated price of $3 apiece, the zinc-air battery-powered, recyclable micro-CPAP devices are intended to be replaced daily.

So far, says Airing business advisor Sharon Sisskind, "the company is making very good progress on building the proof-of-concept prototype." Airing's intended regulatory pathway is the 510(k) as a micro-CPAP device substantially similar to a predicate device. Airing estimates that units will be in production and on their way to eager backers by late 2017.

STAT's Rebecca Robbins reported in September 2015 that some 16 medical device companies have taken a similar crowdfunding route. Robbins noted that while the FDA continues to require that companies follow marketing and advertising regulations, it's unlikely the agency will regulate the practice of crowdfunding.

"Venture capitalists, in general, these days, I think are shying away from medical devices," Marsh says. "We spent some time talking to professional investors and finally got frustrated and said, 'Why don't we do crowdfunding?'" He says there are three reasons to consider crowdfunding: raising funds, gaining external validation, and increasing reach. In an April 2016 video aimed at backers, Marsh said major companies had already contacted Airing with an interest in manufacturing, powering, and/or distributing the device.

Marsh, a longtime inventor, holds 18 US

Photo credit: Nightbalance

Nightbalance vibrates to ensure patients are in the right position for preventing sleep apnea.

patents from the late 1980s to the present; these relate to fuel cells, power chips, and gas storage, among other inventions. Twenty-one additional patents are pending, according to Sisskind. Marsh previously founded venture-backed Integrated **Fuel Cells Technologies, Inc.** in 1999; it filed for bankruptcy protection in 2006.

Airing's technical advisor is Michael Cima, the David H. Koch Chair of Engineering at MIT, and co-inventor of MIT's 3-D printing. Members of Airing's medical advisory board include Chicago White Sox's head athletic trainer Herm Schneider; Jeffrey Bass, an internist with Brigham and Women's Hospital in Boston; and Geoffrey Gilmartin, a pulmonology researcher at Harvard and the medical director of the Beth Israel Deaconess Medical Center Sleep Laboratory. Airing is chaired by Phillip Huyck, a Stanford Law graduate formerly of Credit Suisse First Boston and Trust Company of the West.

REPOSITIONING AID: NIGHTBALANCE

For about half of OSA patients, airway obstruction is positional, and lying on their sides rather than supine can relieve it. Some patients strap tennis balls to their backs, but the Dutch start-up **NightBalance** has developed a gentler option: a small device on the chest that vibrates to remind patients to sleep on their sides. It is for sale in nine European countries and is getting to reimbursement in the Netherlands and Denmark.

"Our aim is to use the naturally occurring arousals that you have when you change position to just remind somebody that they need to continue turning onto their side," explains co-founder and CEO Eline van Beest. "We only need to give a very slight soft subtle hint that somebody needs to continue turning, and people do so."

Founded in September 2009 by van Beest and Thijs van Oorschot, who were then recent graduates of the Delft University of Technology, NightBalance won over €100,000 in prize money in its first year, according to van Beest. Early investors included **Thuja Capital Healthcare** and **Health Innovation** in 2010; they were joined by **Van Herk Ventures** in 2013, the year after *NightBalance* earned CE mark. In July 2016, the 15-employee company announced a €12.5m Series B round led by Dutch venture firms **INKEF Capital** and Gilde Healthcare Partners. Those funds will help the company submit to the FDA for expansion to the US market.

Chairing the medical advisory board is Harvard internal medicine professor David White, a respected researcher on disordered breathing during sleep and former president of the American Academy of Sleep Medicine. A former Phillips Respironics CMO, White is currently also CMO of ApniCure. Medtech veteran Jan Keltjens chairs the board of directors; he holds the same position at **JenaValve**.

Six-month data published in the September 2014 issue of *Sleep* indicated that supine sleep had dropped from 21% at baseline to 3% at six months. Patients also reported feeling less sleepy, though the study lacked a control group. A small randomized controlled trial published in 2015 in *Journal of Clinical Sleep Medicine* compared NightBalance to the "tennis ball technique." While both were equally effective at preventing supine position, compliance was markedly higher and quality of sleep better with NightBalance.

NightBalance now holds patents around the world, whose protections include aspects of the vibration that are tailored to the individual patient. The device's price point ranges between €400-€700. van Beest says NightBalance is open to cooperation with other companies.

AT THE END OF THE NIGHT

Possible limiters to the OSA device market could include reimbursement hurdles and the existing infrastructure of OSA diagnostic and treatment centers, which is closely tied to sleep specialists' incomes.

In 2014, CMS announced it would be reducing payments for CPAP devices, and it requires 90 days of patient compliance data before funding longer periods.

"With respect to payors, they and providers of care are struggling with the uncertainties in the rapid change from volume of procedures to value-based care," Stevens says. "That has caused a dramatic slowdown in the willingness to look at new, even if superior and cost-beneficial, technologies."

As for sleep labs, the traditional gold standard for OSA diagnosis is polysomnography in a sleep lab. But home testing is increasingly recognized as appropriate for many OSA patients; it can be much less expensive and has already been adopted by some health systems, including Kaiser Permanente and the VA.

"The business model for the sleep physician is economically aligned with sleep labs and CPAP prescriptions," Stevens says. "Ultimately, sleep docs are going to have to break their habit of the physical lab."

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