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Inside Israel: The Start-Up Nation Looks East For Investment

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Despite its small size, Israel has grown to become a major player in the medical device industry. The country is famous as the 'start-up nation' and continues to boast an impressive R&D scene which is well supported financially by the Israeli government.

"Innovation is a growth engine for the Israeli economy, it accounts for over 40% of our export and 15% of our GDP and we have a unique model of the government giving money to actively support startup companies," Ora Dar, head of Life Sciences at Israel Innovation Authority tells *Medtech Insight*.

"We have a special granting system but we always grant money in collaboration with the private sector. The highest percentage we grant is 90%, that's for applied research in academia but even the additional 10% must come from the private sector because we want the involvement of people who really look at that outcome and get them involved in the plan and evaluating potential," explains Dar.

The Israel Innovation Authority, previously known as the Office of the Chief Scientist (OCS) of the Ministry of Economy is charged with the country's innovation policy and manages a total budget of ILS1.6bn ($430m) a year to spur innovation. In all, about 30% of that budget goes to the life sciences via its different programs. 20% is usually allocated to Israel's growth incubation programs and early stage companies. The authority also grants money to larger companies for high-risk projects and supports infrastructure for companies including in digital health.

But despite extensive funding programs available, the country's innovation is not immune to ever challenging market conditions. With western countries increasingly tightening their purse strings, Israel is looking to deepen its ties with China. "More Israeli companies are now collaborating with Chinese companies," says Dar. "Obviously to create such activities you have to have an exchange of visits and skills. A lot of Chinese companies are searching for investments in Israel and we are seeing an increase of Chinese investments in Israeli companies."

Strengthening the links between the two countries is actively encouraged by the Israel Innovation Authority and is expected to have great potential for the Israeli innovation ecosystem. "The Chinese are very interested in medical devices and are looking for new technologies to bring to China in order to enhance its healthcare system. They are coming to Israel in search of innovations," says Ruti Alon, former general partner at Pitango Venture Capital, Israel's biggest VC firm.

Alon spent 16 years working in Wall Street before returning to Israel in 1997,

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

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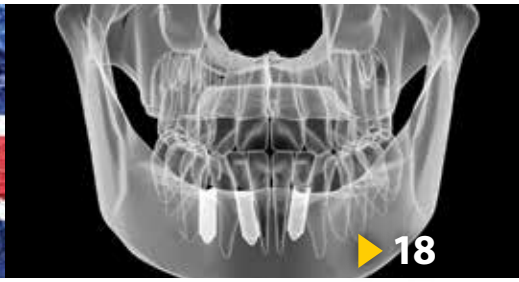

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COMMERCIAL

R&D

Gottlieb At FDA: Industry Will Look For User-Fee Deal Support, Restrained Regulations

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President Trump has tapped former FDA and CMS official Scott Gottlieb to run FDA, an agency that the president recently criticized for impeding innovative new medical products. Gottlieb is likely to favor reducing regulatory burdens for companies. But industry hopes one of his first priorities will be to help push a user-fee reauthorization agreement that was negotiated with the Obama administration through Congress.

The choice comes after months of uncertainty and signs that the president was flirting with making a pick for the commissioner post that would more sharply upend the regulatory system for drugs and devices. But Gottlieb is a known quantity who is expected to reduce burdens on product-makers within the general regulatory framework that currently exists.

Gottlieb, a physician, is generally regarded to have a strong resume for the post. He worked at FDA during the administration of George W. Bush, serving as senior advisor to the commissioner for medical technology, director of medical policy development, and deputy commissioner for medical and scientific affairs at various points from 2003-2007. He also worked as a senior policy advisory at CMS.

Since leaving government, Gottlieb has worked on FDA and CMS policy issues at the American Enterprise Institute and he is also clinical assistant professor at New York University School of Medicine. He has been an outspoken conservative voice on these matters during the Obama administration. He has appeared frequently at FDA and other health-care focused meetings and circulated editorials with ideas for agency improvements. In the realm of medical devices, he has generally pressed for speeding up the approval process and avoiding unnecessarily burdensome trial requirements, such as sham-surgery control groups. *(Also see "Renal Denervation Researcher Argues Sham Control Is Ethically Necessary" - Medtech Insight, 24 Sep, 2014.)*

Gottlieb has also pushed against what he says is overreach by the agency into policing truthful communications about off-label use of devices and drugs, an area where FDA has also received significant pushback from federal courts.

Gottlieb is also a member of the federal Health IT Policy Committee, where he has weighed in on policy proposals related to government oversight of digital and mobile health technologies, an area of increasing focus by device firms, tech companies and FDA. *(Also see "Software Fast Track? US FDA Asks Developers To Envision 'Precheck' Program" - Medtech Insight, 9 Mar, 2017.)* Gottlieb will take over as CDRH works through its proper authorities in the digital space, which have been curbed somewhat by the recent 21st Century Cures Act. *(Also see "'Cures' Bill Circumvents FDA On Medical Software Regs" - Medtech Insight, 30 Nov, 2016.)*

The other individuals that received attention by the Trump administration for FDA commissioner's post veered much further away from the typical candidate. The alternative candidate that received the most attention is Jim O'Neill, an associate of Silicon Valley billionaire and Trump adviser Peter Thiel. O'Neill has advocated removing efficacy as a fundamental standard for approving a new product. *(Also see "Possible Trump FDA Commish Candidate Favors (Much) Lighter Touch" - Medtech Insight, 8 Dec, 2016.)*

The choice of Gottlieb over O'Neill is generally viewed as a victory for the mainstream drug and medtech industry, which does not favor upending the basic structures of the approval process. Sources in industry also suggest that the nomination of Gottlieb is more likely to avoid added turnover and anxiety within the ranks of the FDA product centers.

Gottlieb will need to be confirmed by the Senate, where he is expected to receive support. But FDA watchers still say the confirmation process could take at least six to eight weeks to complete.

The device industry is showing strong support for the nominee, as expected.

"His medical credentials, combined with years of service in leadership roles at both CMS and FDA make him a strong choice to

lead this key agency," AdvaMed President and CEO Scott Whitaker said. "Our industry applauds Dr. Gottlieb's commitment to innovation in medical technology and his recognition of its important role in providing the best care possible for patients."

TRUMP DUMPS ON FDA; USER-FEE REAUTHORIZATION AWAITS

President Trump bashed FDA during his Feb. 28 speech to a joint session of Congress. Trump said the agency was too slow in approving new medical innovations as part of delivering his message that he wants to "slash the restraints" at regulatory agencies. *(Also see "Trump Criticizes FDA For 'Slow' Approvals In Speech To Congress" - Medtech Insight, 1 Mar, 2017.)* Gottlieb, presumably, will be tasked with carrying out that objective.

Trump's message came as the device industry has already signaled big improvements in its experience with FDA in recent years. Total FDA decision times have generally dropped, particularly for PMA devices. And by and large, companies have reported that the device center has been more predictable, communicative and innovation-friendly in recent years.

Further improving the FDA process and ensuring enhancements are maintained remains a significant industry priority and companies will likely view Gottlieb as an ally. But industry's primary strategy for achieving its FDA policy goals is in the user-fee reauthorization agreement reached with the Obama administration and awaiting action by Congress.

The MDUFA IV agreement inked with FDA over the summer includes new performance goals and process improvements (along with increased user fees) that industry says will improve transparency and predictability. *(Also see "MDUFA IV Takes Shape: A Catalogue Of Draft Commitments" - Medtech Insight, 29 Aug, 2016.)* The agreement was transmitted to Congress several months ago, before Trump took office.

But, since then, no public progress has been made. A key Democrat on the House Energy & Commerce Committee recently said that user-fee reauthorization is being pushed behind schedule by the Republican lawmaker efforts to "repeal and replace" the Affordable Care Act. *(Also see "Obamacare Repeal May Be Delaying User-Fee Bills, Rep. DeGette Says" - Medtech Insight, 9 Feb, 2017.)*

Stakeholders expect that having a permanent commissioner in place could push more attention on the user-fee issue in Congress. The current device user-fee program, along with the pharmaceutical and generic drug programs, expire on September 30. But if reauthorization is not approved by mid-summer, layoff notices will need to go out to user-fee-supported personnel at FDA.

Gottlieb played a central role in negotiations that led to the 2007 reauthorization of device fees before leaving FDA at the start of that year. *(Also see "Deputy Commissioner Scott Gottlieb To Leave FDA In January" - Medtech Insight, 18 Dec, 2006.)*

"We look forward to working with Dr. Gottlieb and his team on the medical device user fee reauthorization in the coming weeks and months in our mutual pledge to continued patient access to life-changing technologies," AdvaMed's Whitaker said.

A permanent FDA commissioner is also likely to jumpstart efforts to implement provisions of the 21st Century Cures Act, which includes a breakthrough device provision, among other reforms intended to streamline device reviews. *(Also see "21st Century Cures: Device Provisions" - Medtech Insight, 14 Dec, 2016.)*

Currently, FDA is being run by Acting Commissioner Stephen Ostroff.

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Software Fast Track? US FDA Asks Developers To Envision 'Precheck' Program

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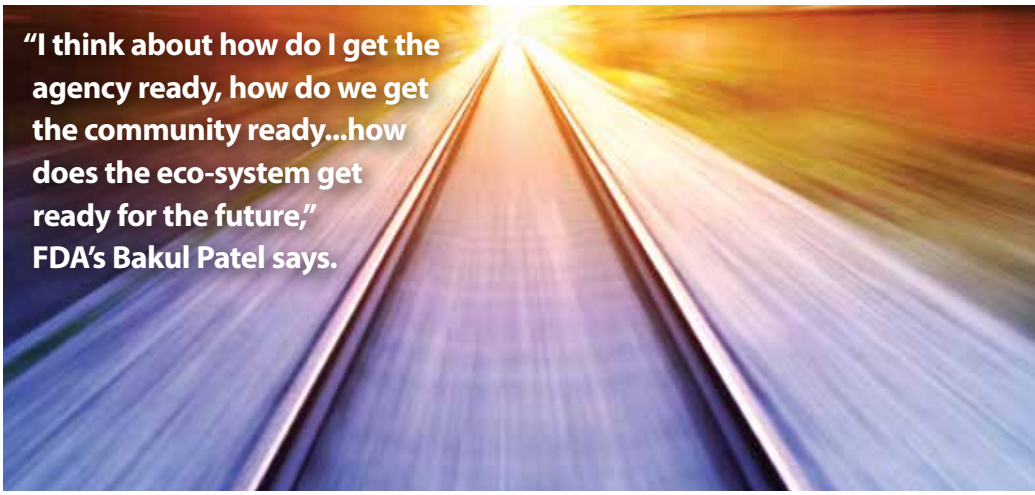
Companies making software that qualifies as a medical device could one day have access to a special fast-track FDA review pathway, but, first, the agency wants input from stakeholders on what such a pathway should look like. If all goes well, the concept could even be applied to products beyond "software as a medical device" (SAMD).

FDA officials have recently been discussing how to deal with unique challenges of product development faced by makers of SAMDs. The matter has been a strong focus among regulators globally. FDA recently issued an International Medical Device Regulators Forum consensus guideline as a draft guidance on SAMDs clinical evaluation. *(Also see "US FDA Plan For Adopting International Software Guideline Draws Industry Concern" - Medtech Insight, 10 Jan, 2017.)* But there are particular considerations within the US. For instance, the recently enacted 21st Century Cures Act laid out statutory barriers around which types of software fall under FDA's authority. *(Also see "'Cures' Bill Circumvents FDA On Medical Software Regs" - Medtech Insight, 30 Nov, 2016.)*

As a result of recent conversations with industry and other stakeholder, the agency has come of up with a concept they're calling FDA Precheck, which could speed the path of SAMD products to market, potentially by relying on a company's track-record to expedite regulatory checks.

The idea is the brainchild of Bakul Patel, FDA's associate director for Digital Health, who unveiled it more broadly to stakeholders at the inaugural Digital Medtech Conference, hosted by AdvaMed in San Francisco on March 2.

"We need to be digital-future ready and that's how I think about … my role in the agency…. I think about how do I get the agency ready, how do we get the community ready...how does the eco-system get ready for the future," Patel told conference attendees.



Patel, the top FDA official on digital health, notes that unlike other devices, SAMDs tend to upgrade and change very quickly, and it is critical that such evolution be allowed to happen at a reasonable pace. He emphasized that, while FDA has its responsibilities, the agency understands that SAMD developers face challenges to bringing their products to market, including the cost of developments and the fact that SAMD products are often a smaller part of larger product offerings.

"FDA gets it, we have lots of people at the agency who kind of think about this and know about this and we get it," said Patel. "There's evolving space about how source code is managed, how software is managed, how software is developed, how software is stored."

He wants FDA to be able to align its regulatory timelines with the timelines companies use in developing software and also sync up that timeline with those of other global regulators.

PRECHECK PROPOSAL

To tackle these issues, Patel proposed the FDA Precheck as a fast-track program that is based on trust. He compared it to the Transportation Security Administration (TSA) Precheck program that allows travelers to get through airport security faster based on prescreening and a level of established trust.

"The experience you get when you have TSA Precheck is different isn't it?" asked Patel, to the majority of conference attendees who signaled that they use the airport security program. "So when you have that experience, what would that experience look like? You still have to go through some detector of some kind to get screened through."

While the concept is at a very early stage of discussion, Patel's asking companies to start conversations within the industry about what would be needed to make a Precheck system work at FDA.

"What if there was a world of FDA Precheck that relies on what the capabilities of a manufacturer are? I don't have the answers to that. What does that look like, what does that mean? We need to explore that together and that's my ask for all of you," said Patel.

He said members of industry can provide feedback by reaching out to him or emailing FDA's digital health office, but he recommends first talking to the industry associations so they can brainstorm ideas collectively and present aggregated proposals to the agency.

"It's probably more efficient if organizations or groups collectively [contact me]," said Patel to *Medtech Insight* after his talk. "If I get one at a time it'll be very time consuming… but I'm happy to get that."

But the potential pathway has to be "palatable" to all stakeholders, including FDA, he said.

PROMISE SEEN, BUT DETAILS NEEDED

Patel joined a panel at the conference that included Ashwin Pushpala, founder of Sano, a startup developing a glucose monitoring mobile app; Larry Carrier, head of regulatory affairs at **Verily Life Sciences LLC**, formerly Google Life Sciences; and Nathan Brown, a partner at Akin Gump Strauss Hauer and Feld and former FDA counsel. The panel was moderated by Zach Rothstein, AdvaMed associate vice president for technology and regulatory affairs.

Pushpala said the impact of a Precheck program on startups like Sano could depend on how the program is structured. He pointed out that company's like his don't have a history built up with FDA that may be needed form the necessary trust that would underlie a Precheck pathway.

But due to the prospect of reducing regulatory burdens, the proposal has promise to increase investor interest in digital health, Pushpala said.

Verily's Carrier says if the program adds predictability, it could be advantageous to SAMD companies and allow them to efficiently shift resources internally.

"If we know the elements of the Precheck we can kind of have a better understanding of what we need to do to get the product out the door," he said.

PROCEED CAUTIOUSLY, ATTORNEY SAYS

But attorney Nathan Brown warned that there could be some downstream regulatory implications from such a program.

"Right now, that FDA approval or clearance carries a lot of benefits both within our system and worldwide, things like being able to get on the market faster in other countries," Brown said.

"For a PMA device you have certain benefits for preemption [from personal injury suits], that you wouldn't inadvertently want to lose," Brown cautioned.

Part of the challenge, as stakeholders talk about developing the pathway, will be to ensure that those benefits are not lost.

Brown also notes that if the Precheck system will be based on a company's track record, there should be considerations for when well-intentioned companies make mistakes. That should not lead to an automatic loss of the trust FDA has instilled in them, he suggested.

"If the concept is, it's based on track record and there are robust systems in place. you have Precheck, how is that system dynamic?" he asked. "Even experienced companies run into problems so how does the system make adjustments so they don't lose [the] trust factor?"

Brown also pointed to the provisions in the latest device user-fee reauthorization agreement that are aimed at reducing reporting requirements for certain device malfunctions that are well-known to the agency. *(Also see "MDR Reporting: FDA Embraces Adverse Event Summaries Under MDUFA IV, But Flouts Similar FDAAA Mandate" - Medtech Insight, 5 Jan, 2017.)*

"You could easily see a Precheck program where you have certain companies that have met certain requirements to have something similar where you could say, instead of reporting well-known malfunctions or reporting well-known adverse events that everybody knew and understood, focus the energy on the types of events that are unusual, new, the ones that are really affecting safety in a new way," he said.

"It seems like Precheck is the kind of program where you could develop a way to do that, that is so broad as to...reduce an important mechanism of regulatory oversight, to say that companies that have a track record of really investing in post-market surveillance, you sort of shift that burden from focusing somewhat on reporting to focusing on actual surveillance and remediation."

EXPANDED APPLICATION?

FDA in recent years has also been working to develop a new paradigm where some devices could reach the market sooner based on less pre-market data but contingent on strong post-market surveillance. This has been a catalyst for development of the National Evaluation System for Health IT (NEST), a nascent system for establishing networked registries that FDA hopes will improve monitoring of products over a long period after approval or clearance. *(Also see "Real-World Evidence User-Fee Funding Praised At FDA Meeting" - Medtech Insight, 2 Nov, 2016.)*

Patel says the fact that software has the capability of collecting more patient data than traditional medical makes it ideal to take advantage of the new paradigm.

While the FDA Precheck program is currently being discussed only for SAMDs, Patel isn't discounting the possibility that it eventually could be applied more broadly to other device areas. For now, he says, SAMDs are the "fastest moving piece" in the medical device space and there is a lot of consensus on how to develop them, which makes the products ripe for such an expedited pathway.

"I'm purposefully keeping the scope narrow to software as a medical device," he told *Medtech Insight*. "Otherwise it gets so big and unwieldy that we won't solve anything."

Patel says there will be a broader and larger public conversation on the topic, but doesn't want to have it yet in a public forum until more details have been hashed out. He says it's possible that after a preliminary interaction with industry, there may not even be an FDA Precheck and the concept could morph into something else.

"I wanted to start something and I think people are getting excited about it...but I want to see it evolve a little bit before we have a larger public dialogue, because then we will have to go through our regular process of public engagement and commenting."

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WATCH

Check out a video of the Digital Medtech Conference panel with Bakul Patel at http://bit.ly/2mqdWEo.

FDA Lists Hundreds Of Devices For 510(k)-Exemption

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Manufacturers won't need to submit 510(k)s on devices ranging from surgical lamps to tests used to screen employees for drug use if a March 13 proposal from US FDA goes into effect.

The *Federal Register notice* lists several hundred device "Code of Federal Regulation" categories and a total of 1,003 class II device-types, including specific allergen tests within a particular CFR category, that FDA believes would be safe to market without 510(k) submissions. FDA says the devices "are sufficiently well understood and do not present risks that require premarket notification review to provide a reasonable assurance of safety and effectiveness."

Last year's 21st Century Cures Act requires FDA to publish a list of class II device types that could be designated 510(k)-exempt within 90 days of the law's Dec. 13 date enactment.

A 60-day comment period will follow, and the exemptions should be made final within 210 days of Dec. 13, 2016, or by July 11. Going forward, FDA must release lists of devices that could be made 510(k) exempt at least every five years. *(Also see "21st Century Cures: Device Provisions" - Medtech Insight, 14 Dec, 2016.)*

Some of the exemptions apply only to specific device types within a broader product category. For example, an exemption of the endoscopic magnetic retrievers is limited to single-use products. FDA says it makes distinctions like this when the safety information only supports exempting a subset of devices within a broader category.

Many of the device types listed can be classified into several broad categories, including: assays used by employers and insurers to test for drugs; blood-test supplies such as white-cell and red-cell controls; denture accessories; and lights used during diagnostic procedures and surgeries, as well as medical tables and drapes. The list also exempts allergens such as pollen and animal cells that are used to test the immune system.

The proposal doesn't exempt listed devices from all regulatory oversight, FDA emphasizes. Products still must meet good manufacturing practice requirements, as well as packaging and labeling rules. In addition, manufacturers still need to register their establishments and list the devices with FDA.

Comments on the proposal are open through May 15 under docket no. FDA-2017-N-1129.

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Brexit And The Regulatory Question: Where Are We Now?

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There may still be much uncertainty about how Brexit is going to play out in the UK and what impact it will have on medtech regulations, but Phil Brown, director of technical and regulatory at the Association of British Healthcare Industries (ABHI), says he feels more positive now about the UK's future in the EU medtech regulatory space than he did six months ago.

"I can say I am optimistic because ABHI has had extremely positive discussions with the Medicines and Healthcare products Regulatory Agency on their visions post-Brexit," Brown told *Medtech Insight*.

These assurances are only verbal, he noted, but, in his view, logic would dictate that the UK uses the upcoming new Medical Device Regulation (MDR) rather than any other system.

"Reading between the lines" of what is generally being discussed at the moment in UK circles, Brown seems confident that the country is heading towards a direction where the MDR and the IVD Regulation (IVDR) are likely to stay.

His words come after Richard Phillips, director of healthcare policy at ABHI, told *Medtech Insight* in a recent interview; "I think there is unanimity that if we end up with a sovereign regulatory system in the UK, however good it is, that that will have no util-

LISTEN

Phillips and ABHI's chief operating officer Nishan Sunthares also discuss the potential regulatory and trade scenarios for the UK medtech industry in this recent podcast http://bit.ly/2mocfqi

ity beyond our own jurisdiction and not be very helpful. It will become another hurdle."

But, of course nothing is definite yet. There will be certainty only when the government says exactly what will happen with regards to regulation for the medtech industry and that won't happen until probably sometime early this summer, Brown said.

He acknowledged that ABHI has indeed been thinking about multiple regulatory options, as he had revealed in an interview with Medtech Insight last August. But, since then, the focus, he said, has been on the need for a mutual recognition of CE marking between the EU and the UK.

> "Our thought processes and needs, particularly in terms of regulatory, may be very different to the needs of the pharma industry amongst others," ABHI's Phil Brown says.

"We put together different options because that is what the political situation demanded. But once we really looked at it closely, it made us realize that there is not really any other logical option," he said.

THE BIGGER PICTURE

But there are still the questions of what the position will be of the other EU countries, angered by the UK's decision to withdraw from Europe, and how much flexibility the EU will allow the UK if it takes a "hard Brexit" approach? Also, how does medtech fit with the UK's overarching policy for going forward post-Brexit?

"Our thought processes and needs, particularly in terms of regulatory, may be very different to the needs of the pharma industry amongst others," Brown admitted. Indeed, the best way forward, he suggested, may be easier to tease out for medtech than other life science industries with which medtech is being considered in Brexit negotiations

This general uncertainty, he added, will persist until the government decides the way forward for all industries covered under the UK's Brexit Life Sciences Strategy.

The UK is entering into a broad negotiating phase and clarity is still required. Industry needs to know how "hard" a Brexit the country will be pursuing and the repercussions of the approach. According to Brown, one area where confusion may persist, even if the UK continues with the MDR and the IVDR, is the status of UK notified bodies.

NOTIFIED BODIES

"We need certainty over 'if' and 'how soon' notified bodies can be accredited against the MDR and at when they can start to certify companies," Brown said.

What is more, the capacity issue within the notified body system in general is already becoming increasingly critical. There are an increasing number of discussions now with ABHI members concerning timeliness of certification, audits, audit results and reports, according to Brown. He added that this increasingly acute notified body capacity issue has been put to the attention of decision-makers. The European medtech association, Medtech Europe, is holding a meeting in the middle of March to discuss the topic.

The concerns of notified bodies mirror the discussions the medtech industry is having, said Brown. Notified bodies need to know:

- If they need to gear up for the new Medical Device Regulation;
- When they need to be ready;
- The timeliness of CE marking certificates, especially during the transition period from the current directives to the new regulations; and
- When device companies can approach notified bodies.

UK notified bodies need to know exactly which path they need to take. "There are concerns, otherwise, of the possible risk that these notified bodies could be told suddenly after two years that they are no longer relevant to the EU system because they are based in the UK," Brown stated.

"So we are all living with that uncertainty around the UK notified bodies. We are being guided by the MHRA and the policy people, and feel optimistic by what they are saying," he said, adding that there are precedents of having notified bodies operate beyond the EU borders, for example, in Switzerland and Australia.

THE NEGOTIATING TEAM

When it comes to the soon-to-be-adopted MDR and IVDR, ABHI has been and continues to work closely with the MHRA and its European counterpart association, Medtech Europe. Brown says that ABHI particularly welcomes the clarification in the final, recently released text of what happens during the transition period in between the MDR first taking effect and when the MDR is fully applicable in 2020 and beyond. *(Also see "Comply With EU MDD Or MDR? Your Multi-Year Decision Is Beset With Hazards" - Medtech Insight, 2 Mar, 2017.)*

Brown also explained that the ABHI Regulation implementation group will become more active once the MDR has been published.

He added that the association wants to move away from new the regulations being treated as an individual pillar and look more at how they impact the different areas of the business environment, and to view the MDR as a business opportunity rather than a regulatory burden.

ABHI plans to:

- Set up groups to maximize overlap potential, for example, in the areas of regulatory and manufacturing; regulation and clinical; and regulation and policy; and
- Set up a manufacturing and operations group.

The association is also running a series of webinars on MDR issues. The most recent, Quality management systems and the MDR, was held on Mar.9. Other subjects that are likely to be covered running up to June are likely to include clinical data; pre-market and post-market requirements; implementation; and notified bodies.

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"When I arrived it was an exciting time. The Israeli life science industry was at its early stages and growing fast," she says. After 35 years in the medtech industry, Alon recognizes the rapid changes occurring in the medtech market.

"In the past, if you were a medical device startup and your technology was deemed valuable, large companies would acquire it, even in early stages. Today, the winds have changed. Big companies are seeking technologies that have gone through regulatory clearance or are already in the commercial phase."

"Since companies and investors are taking less risks with investments, there's been an increase in fund flowing into digital health technologies which are perceived as being less expensive to develop," she explains. Alon says the markets can't remain stagnant anymore and expects to see a rise in medtech M&A activity after a steady decline in recent years. "For a while, in order to cut costs, medtech companies were forced into mergers. Now in order to insure future growth, they will need to acquire new technologies with proven efficacy, rather than solely relying on [sales growth from the] emerging markets," says Alon.

Managing partner of Tel Aviv Venture Partners and digital health expert Benny Zeevi says that "most of the funding now in the life sciences is not coming from Israel, it's coming from abroad from corporate financing, foreign VCs, Chinese or Japanese investors."

"Less than 15% is coming from Israeli venture capitalists and there are not many angels in the Israeli life sciences industry," he tells *Medtech Insight*. Further underlining Dar's comments on the increasing significance of China's role in Israeli medtech, Zeevi adds that China has invested "billions" in Israeli life sciences over the last five years and acquired many Israeli companies. Many of the Chinese investors want the technology to be implemented in China and this is a huge opportunity for Israel. However, he warns that the Chinese government is beginning to block Chinese money coming out of the country, so this could be a future challenge for investors to overcome.

Israel's Hi-Tech Incubator Program

The government's hi-tech incubator program is one of the key sources of start-up funding in Israel. The program was founded in 1991 and today there are 18 incubators across the country, all of which have been privatized. The incubators function as a center for entrepreneurship and nurture companies from seed to early stage, thereby minimizing the risk to future investors. They also offer a supportive framework for the establishment of a company and development of a concept into a commercial product, with many companies' R&D facilities based at the incubator.

ADVANCING IN DIGITAL HEALTH

One field experiencing a significant boom in development is digital health, according to Zeevi, who says Israeli innovation within digital health technologies is rising fast. "There are now more than 500 companies in Israel dealing with health IT and digital health," he says.

"Digital health is a big basket, covering wearables, health applications, remote monitoring, telemedicine, telehealth, elec-

ORA DAR
Head Of Life Sciences, Israel Innovation Authority

RUTI ALON
Former General Partner, Pitango Venture Capital

BENNY ZEEVI
Managing General Partner, DFJ Tel Aviv Ventures

DAN SHWARZMAN
CEO, MindUP

LIOR TEITELBAUM
VP Business Development, MindUP

STEVE RHODES
CEO, Trendlines

ZOHAR GENDLER
Managing Partner & CEO, NGT³

"There's a lot of innovation out there and unmet clinical needs. Our focus in digital health is on treating chronic diseases, precision medicine and applying preventative medicine to screen for diseases and better management of population health. Another area that is of interest to us is the democratization of care, transitioning healthcare to point of care and to the patient's home," MindUP's Lior Teitelbaum says.

tronic health record, enterprise solutions, data analysis, artificial intelligence and cybersecurity. Israel has companies in all these different subsectors of digital health. The advantage in Israel is that these technologies can be tested quite easily because of our large HMO's which are open to new technologies, so the opportunities for business are out there."

"Another huge [digital health] development opportunity for Israel are the emerging markets in Africa, there are more than 650 million people in the continent and governments in Africa are becoming financially stronger and mobile phones are more popular than running water in Africa. Mobile phones can be used in remote areas for healthcare solutions and because the development process in Israel is less expensive than in the US, we are seeing more investors in technologies for Africa." Health IT is set to be one of the subjects explored at the MIXiii BIOMED annual conference, Israel's leading international life science industry conference. The conference, now in its 16th year, will be held in Tel Aviv in May and is expected to attract over 6,000 participants. This year the leading theme is aging and Alon and Zeevi, co-chairs of the event, divided the conference into nine different tracks to cover a broad range of subjects all related to aging and longevity

"We deal with subjects at the cutting edge of science as being dealt by the industry," says Alon. "We also have leading physicians and researchers from academia, yet the focus is on applied science."

"BIOMED also serves as the annual meeting place for Israel's healthcare industry with colleagues from across the globe. The meeting offers an opportunity for forming new partnerships and strengthening existing business relations between the Israeli and international life science industry." (See box at the end of the article for more info on MIXiii BIOMED 2017).

MINDUP: MEDTECH INDUSTRY/INVESTOR JV

MindUP, a new kid on the incubator block aims to capture this wave of digital health innovations. The digital health-dedicated incubator was established in March 2016 as a joint venture between **Medtronic PLC**, **IBM**, Pitango, **Rambam** and Impact First investments.

"Israel is well adapted to digital health needs as it was one of the first countries to adopt electronic records. The HMO's and medical providers in Israel have been working with electronic records for already two decades," says Dan Shwarzman, CEO of MindUP. "So the infrastructure for extracting and analyzing data is available. There is also the mindset of working electronically and the data sets can be used for research and development."

MindUP signed its first portfolio company, **Hemonitor,** in Jan. 2017. The startup isdeveloping an autonomous, continuous and non-invasive ultrasound-based system for patient monitoring. "Part of the things we are looking for is innovative and riskier products that hold promise," explains Lior Teitelbaum, VP of business development at MindUP. "There's a lot of innovation out there and unmet clinical needs. Our focus in digital health is on treating chronic diseases, precision medicine and applying preventative medicine to screen for diseases and better management of population health. Another area that is of interest to us is the democratization of care, transitioning healthcare to point of care and to the patient's home."

"Digital health has seen a surge over a few years and some of it has to do with the increased interest in potential, but now there's a higher barrier and proof is needed to show usability, user traction and actual clinical value or healthcare service."

MindUP say digital health entrepreneurs entering the market can expect to face the many challenges confronting an early stage company in this field. "Firstly, the regulatory environment is continually being shaped and IP is not easy to gain," says Shwarzman. "Another major challenge is related to the market and the ability to execute. With digital health you're looking at multiple customers and different customers/targets for the same product and sometimes different geographies that require different versions of the product. All of these factors can complicate the route to market."

"In addition, there is the navigation of payment and reimbursement structures," he continues. "More customers also want to see data and proof of efficacy and see that products work at their own specific hospital first. Plus, small digital health players have to contend with the intensifying competition, with more established companies entering this field. We also see challenges with data privacy, security and compliance with specific country regulations," adds Shwarzman.

The ever growing presence of Chinese investors has also touched Israel's digital health scene.

"China is certainly a dominant player in the field. It's a very attractive market as the numbers in China are huge and developing fast, and they digest new technologies fairly fast. They are also making steps to catch up with the US so there's a great opportunity and very specific market needs," says Shwarzman.

Although MindUP began operations less than a year ago it has already evaluated over 150 projects internally and aims to attract entrepreneurs from across the world. "As long as entrepreneurs are willing to come and register the company in Israel and spend at least two years in Israel, we're more than happy to host overseas entrepreneurs," says Shwarzman.

TRENDLINES: INNOVATION COMMERCIALIZATION

Trendlines, one of the larger incubators in Israel, was founded in 2007 and now has 30 medtech companies on its books. "What we found over the years is that when young tech based Israeli companies fail it's usually not because of failure on the technology side or lack of market need, but rather because of poor execution on the business side," says Steve Rhodes, Trendlines CEO and Co-Founder.

"We're in the business of commercializing innovation. Our business is to start companies. We are early stage investors and start around 8-10 companies each year," says Rhodes.

"We're typically the very first money into a company and there's a lot of risk inherent in the companies we invest into. So in order to reduce the risk of investments, we use incubators to surround the companies with support – we provide capital but we are also deeply involved."

Trendlines' portfolio companies are supported by a team of 40 people across the business development process. In 2015, Trendlines listed on the Singapore Stock Exchange in a bid to tap into the coveted pool of Asian capital. "We chose Singapore for several reasons," said Rhodes. "First, we felt that Trendlines was not ready to list on the Nasdaq and we had been expanding greatly in the last five years in Asia. When we visited Singapore, we found an orderly market that was very well regulated with no 'monkey business' and a lot of Asian investors, including Chinese capital."

Singapore welcomed the listing as part of the government's initiative to encourage business enterprise in the country. "Life in Singapore is so good and comfortable that there's not a lot of entrepreneurship going on there," jokes Rhodes.

To date, Trendlines has sold six of its portfolio companies to large international partners including **Baxter International Inc., Covidien** (before it was acquired by Medtronic)**,** and **Teleflex Inc.** One of its portfolio companies that is currently gathering pace is **ApiFix**, a correction system for treating Adolescent Idiopathic Scoliosis (AIS). The implant incorporates a ratchet mechanism that is inserted through a small incision in the patient's back and corrects the deformity over several months.

"As with many new technologies, people can be resistant to change so we are rolling out this product very gradually because the market is very conservative," explains Rhodes "Of course when you're implanting something into the spine of a young girl, it's wise to be cautious but this is one company that we believe is destined for great success."

The ApiFix device has been used on more than 110 patients in Israel and in eight European countries and is edging closer to approval by the US FDA. Trendlines believes the market for the ApiFix system could be worth around $1bn. "Even during economic downturns when M&A is usually affected we haven't been impacted as we sell niche products that address specific needs," says Rhodes.

Other Trendlines companies holding particular promise include **Gordian Surgical**, developers of a trocar with integrated closure system and **Leviticus Cardio**, a wireless system for VAD implants.

Key Themes at MIXiii-BIOMED

- The impact of aging on population health and world economy
- Longevity: genetics and epigenetics
- Precision diagnostics and medicine
- Regenerative and cell therapy
- Robotics and aging
- Age-related diseases: cancer, neurodegenerative diseases, diabetes, congestive heart failure, hypertension and more
- Health IT, digital health and cybersecurity
- Continuum of care for the elderly patient
- From academia to Industry as related to aging and age related issue

For more information about MIXiii-BIOMED, visit http://kenes-exhibitions.com/biomed2017/

MIXiii-BIOMED, May 23-25, 2017, Tel Aviv, Israel

NGT³: STRENGTHENING JEWISH-ARAB TIES

But innovation is not the only name of the game for Israeli incubators. Nazareth-based incubator NGT³ is using its incubator program as a way to forge relationships between the Jewish and Arab communities. An early-stage investment entity structured as a venture capital fund, NGT³ is focused on medical device and life science technologies. "As a technological incubator, we are unique in many ways," says Zohar Gendler, CEO of NGT³. "We have 21 partners from around the world including the US, Spain, Israel and one from India. All the partners in NGT³ support the capabilities and knowhow of our portfolio companies."

"Another one is our social agenda - our location is not a coincidence. Nazareth is the largest Arab city in Israel's Galilee and we try to support inventors and investors from the Israeli-Arab- community. The best way for Israeli-Arabs and Jews to live together as equals is to work together. At NGT³, we are trying to bridge between these communities. This is one of the main reasons I joined NGT³."

NGT³ currently has ten companies in total, with three medical device companies in its portfolio – **Aqueduct**, a cervix dilator, **Guide In Medical**, developing a guided intubation system and **Eio Bio**, a medical device for the prevention of post-surgical adhesions.

Gendler says: "In medical devices now, the large companies are looking first and foremost to see market acceptance. In fact, they want to see significant market acceptance before purchasing companies. But despite this, there is still money out there for innovative technologies."

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M&A DEALS ANALYSIS:

February Sees Billion-Dollar Buys Bite

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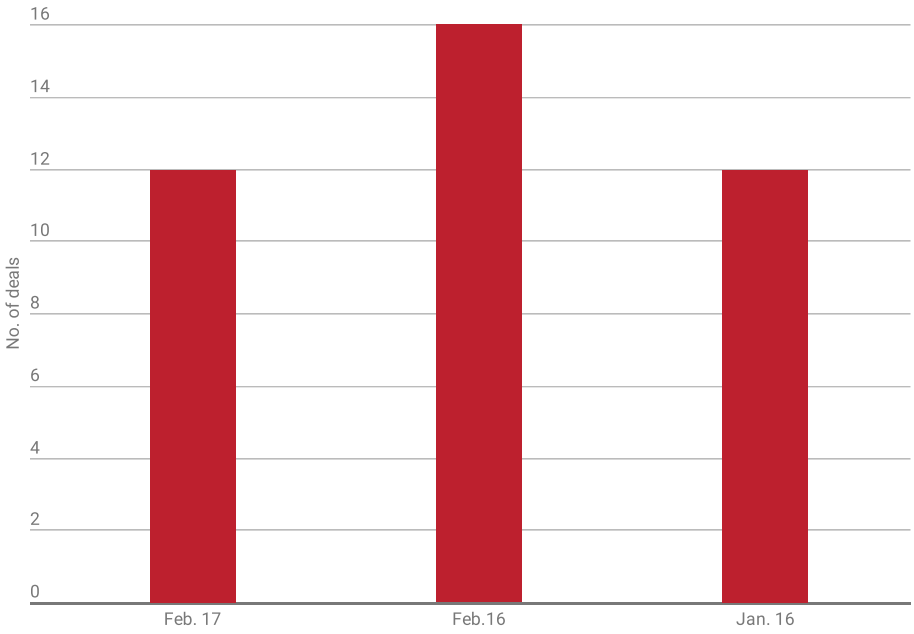
After a lackluster start to the year, the medtech market sprung to life in February as companies started to spend big. *Medtech Insight* recorded 12 medtech M&A deals in February, on par with January's volume but down from 16 in February 2016. (See Figure 1.)

While the biggest value deal in January was **Hill-Rom Holdings Inc.**'s $330m acquisition of **Mortara Instrument Inc.**, last month saw a hat-trick of billion dollar deals, mirroring the trend seen a year ago. *(Also see "MNA Analysis: Abbott And Stryker Make Big Deals In Slow Month" - Medtech Insight, 8 Mar, 2016.)*

FIGURE 1

M&A deal volume Feb. 2017 vs Feb. 2016 vs Jan.16



Source: Medtech Insight M&A deal tracker

BILLION DOLLAR BUYS

In the biggest buy of the month, Botox-maker**Allergan PLC** agreed to pay $2.47bn in cash to acquire 'fat-fighter' **Zeltiq Aesthetics Inc.**Zeltiq's flagship product is the US FDA approved *CoolSculpting* body-contouring system which freezes and removes fat cells. The company expects to generate $420m in revenues in 2017, Allergan said the deal would start boosting its earnings before the end of the year. "Medical aesthetics is probably one of the best and fastest growing businesses in the pharmaceutical arena," said Brent Saunders, Allergan's CEO, on a call with analysts to discuss the deal. Allergan said it estimates that body contouring is a $4bn market and expects the acquisition to close in the second half of 2017.

A day later, women's health solutions specialist **Hologic Inc.** announced its efforts to get a slice of the medical aesthetics pie via **Cynosure Inc.** Hologic will pay $1.65bn for the business, which markets a range of laser systems for aesthetic indications, including vaginal rejuvenation, body contouring, hair removal, and skin revitalization, among other things. *(Also see "Hologic Stitches Medical Aesthetics Into Women's Health" - Medtech Insight, 15 Feb, 2017.)* The acquisition gives Hologic entry into medical aesthetics for the first time. Hologic CEO, Stephen Macmillan said during a Feb. 14 conference call that Cynosure provides access to a "large, growing opportunity," in the aesthetics field. The deal came together after Hologic sold its blood-screening business to partner Grifols for $1.85bn. *(Also see "Blood Brothers No More: Hologic Unloads Blood-Screening Business To Partner Grifols" - Medtech Insight, 15 Dec, 2016.)*

The third billion-dollar deal in February came from **Integra LifeSciences**, which made a "binding offer" to acquire **Johnson & Johnson**'s **Codman Neurosurgery** business for $1bn in cash. Codman Neurosurgery is part of J&J's Depuy Synthes group and holds a portfolio of devices focused on advanced hydrocephalus, neurocritical care and operative neurosurgery. Integra said the buy would complement its existing neurosurgery portfolio and boost its global reach. *(Also see "Integra Aims To Bolster Neurology Portfolio With J&J Codman Buy" - Medtech Insight, 16 Feb, 2017.)*

At the other end of the spectrum, in a much more modest deal,**Teleflex Inc.** agreed to acquire Canadian medical device company **Pyng Medical Corp.** for cash consideration of approximately $8.5m. (See Figure 2.)

Pyng is a developer of trauma and resuscitation products for front-line critical care. Its portfolio includes innovative sternal intraosseous (sternal IO), pelvic stabilization and tourniquet devices designed for both the military and civilian markets.

In a statement, Ronald Blanck, chairman

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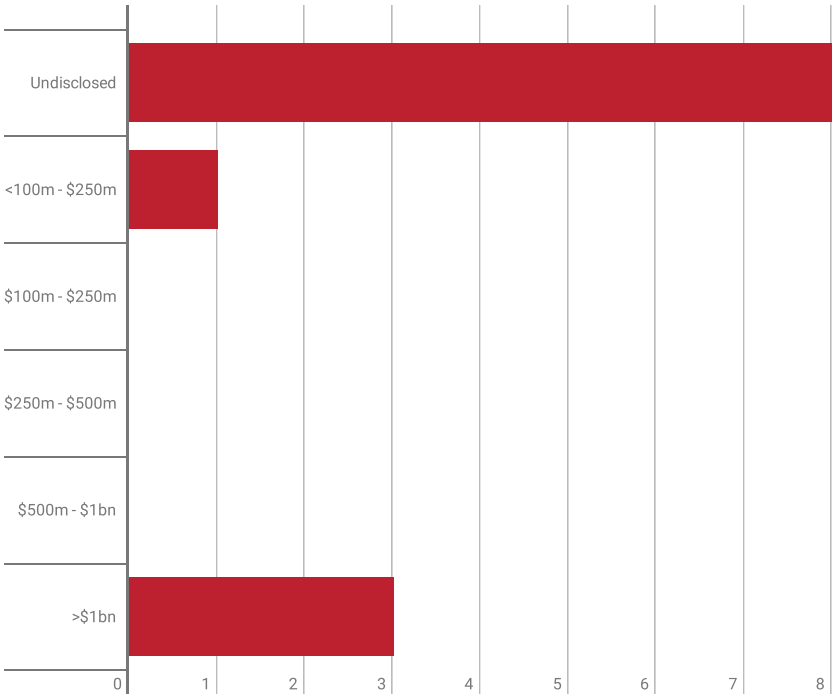
For more details about M&A deals in 2017 and previous years, go to Medtech Insight's M&A deal tracker: https://medtech.pharmamedtechbi.com/datasets/mna

FIGURE 2

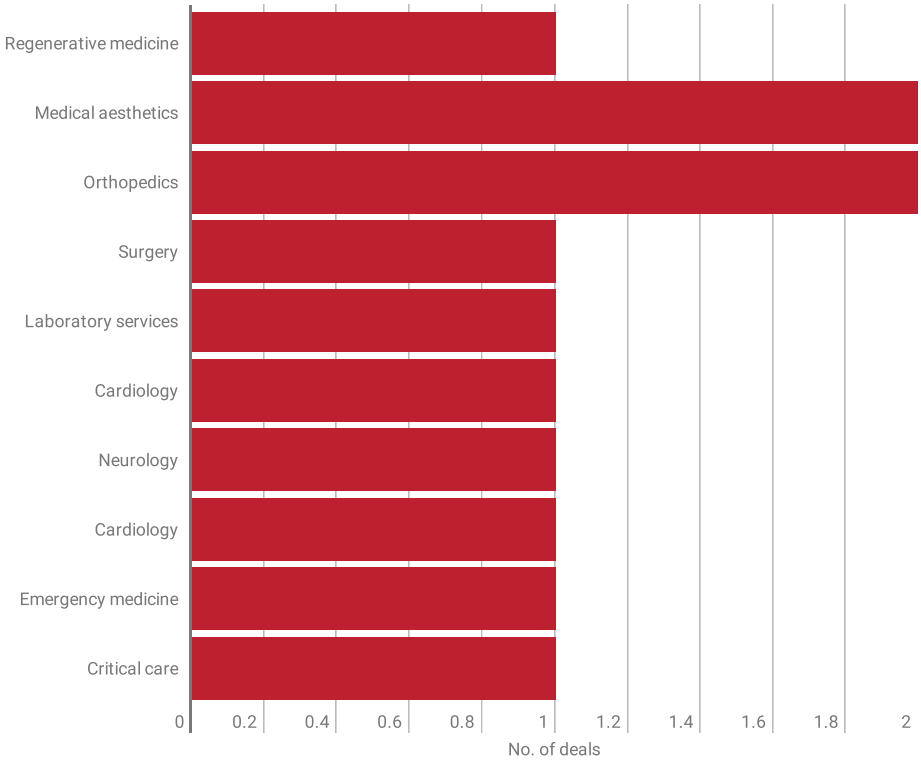
February 2017 M&A by value



Source: Medtech Insight M&A deal tracker

FIGURE 3

February 2017 M&A by product type



Source: Medtech Insight M&A deal tracker

of Pyng said: "Pyng has a highly innovative portfolio of proprietary emergency medical products. Given the capital and marketing expertise required to fully exploit these products, we believe this is an attractive result for our shareholders and that Teleflex will be able to achieve significant market potential for Pyng's products."

By sector, medical aesthetics and orthopedics picked up two deals apiece. The month was surprisingly absent of deals in IVDs, but saw regenerative medicine, surgery, cardiology, critical care, laboratory services, neurology, critical care and emergency medicine grabbing a deal each. (See Figure 3.)

In orthopedics,**ChoiceSpine**, a privately held spinal fusion device manufacturer acquired the spinal assets of **Exatech**, a developer of bone and joint restoration products for extremities, hip, knee and spine. Swiss orthopedics manufacturer **Medacta** announced its acquisition of Austrian distributor **Vivamed**. Medacta said the acquisition aims to strengthen the company's presence in Austria and support growth of its expanding product portfolio.

In the field of interventional cardiology, Europe's fourth leading player in the transcatheter aortic valve replacement market, **Symetis SA** finally expanded into mitral valves with its maiden acquisition, buying preclinical-stage firm **Middle Peak Medical Inc.** Middle Peak Medical is a private US and German medical device developer of a transcatheter mitral valve repair system. Symetis CEO Jacques Essinger said what attracted him to MPM's technology was that it had already been proven in another product, the *MitroFix* mitral valve restoration system. *(Also see "Europe's TAVR No. 4 Buys Into Mitral Valve Space" - Medtech Insight, 14 Feb, 2017.)*

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VC DEALS ANALYSIS:

Hemodialysis Stands Out In February 5-Year Famine

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February saw 20 venture financing deals cross *Medtech Insight*'s news desk, representing a significant drop from January's 26 deals and a dip from the 22 transactions recorded in February last year.

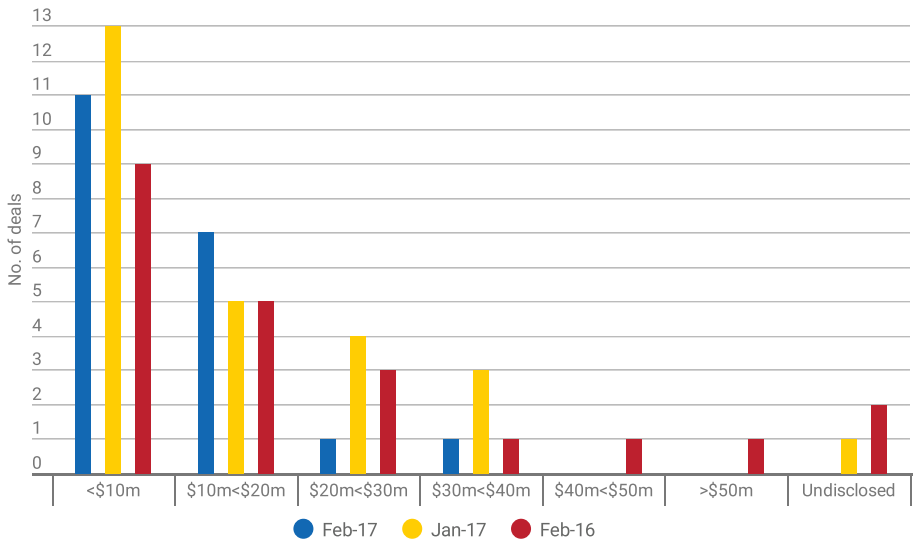
But while a modest deal volume doesn't always correlate with an equally modest deal value, the lack of fundraising rounds north of $40m meant that the total raised in February only amounted to $201.8m, the lowest level seen in five years. This is a 45% drop from the $369.5m raised in February last year, when there was a single $100m round that month to boost the total takings. (See Figure 1 and Table 1.)

DISINFECTION ROBOTS GRAB TOP DEAL

The biggest round in February 2017 was a $38m later-stage growth equity financing raised by disinfection technology specialist Xenex Disinfection Services. (See Table 2). The Texan firm's LightStrike robots help to combat hospital-acquired infections by using pulsed xenon to create high intensity UV light that can destroy HAI-causing germs in five minutes. Established in 2008, Xenex said its robots are already being used in around 400 hospitals in North

FIGURE 1

No. of venture financing deals by amount raised, Feb 2017 vs Jan 2017 vs Feb 2016



Source: Medtech Insight VC deal tracker

TABLE 1

February total deal value, 2013-2017

	FEB 2013	FEB 2014	FEB 2015	FEB 2016	FEB 2017
Total amount raised ($m)	277.9	248.5	252.4	369.5	201.8

Source: Medtech Insight VC deal tracker

TABLE 2

Top 5 VC Deals By Amount Raised, February 2017

RANKING	COMPANY	BASED IN	PRODUCT/ THERAPY SECTOR	AMOUNT RAISED	FINANCING ROUND	TOTAL INVESTMENT
1	Xenex Disinfection Services	TX, US	Sterlization devices	$38m	Undisclosed	Undisclosed
2	Motus GI	Tirat Carmel, Israel	Gastroenterology	$25.6m	Part of an expected $30m round	Undisclosed
3	Allurion Technologies	MA, US	Obesity management	$19m	Part of an expected $27.3m round	Undisclosed
4	HemoSonics	VA, US	IVD	$15m	Undisclosed	Undisclosed
5	Avenu Medical	CA, US	Hemodialysis management	$13.1m	Part of an expected $16m round	Undisclosed

Source: Medtech Insight VC deal tracker

America, Europe, Africa and Japan. Hospitals using LightStrike have published outcome studies in peer-reviewed journals showing 50-100% decreases in *C difficile*, methicillin-resistant *Staphylococcus aureus* and surgical site infection rates, according to the company.

The $38m round was led by well-recognized healthcare venture backer Essex Woodlands, and included the participation of existing investors Malin Corporation and Tectonic Ventures. The proceeds will be used to expand product sales and expand internationally, as well as advance its R&D programs.

AV FISTULA GRABS INVESTOR INTEREST

February's venture dollars went to a diverse spread of product/therapy sectors, as reflected in the Top 5 deals. Squeaking in at No. 5 is **Avenu Medical**, a company that raised around $13.1m in the first tranche of what it hopes would be a bigger $16m round. The Californian firm already has a CE-marked product, the *Ellipsys* vascular access image-guided catheter system designed to percutaneously create arteriovenous (AV) fistulas for hemodialysis access.

The AV fistula is a surgically created vessel which connects the artery and vein and it is through this vessel that the patient is hooked up to the hemodialysis machine and allows the patient's blood to be removed, dialyzed and returned to the body. According to another start-up, Singapore-based **Advent Access**, which is also developing AV fistula technology, a third of the costs of managing dialysis patients is not related to the dialysis technology itself but to vascular access, specifically access to the AV fistula. *(Also see "SSB Start-Ups" - Medtech Insight, 30 Aug, 2016.)*. The care and management of this vessel is important as there are only a limited number of sites where this fistula can be created – which likely explains the demand for technologies such as Ellipsys that could help physicians create the fistulas with as little complication as possible.

There were two other financing deals related to companies with AV fistula management technologies in February. **Flow Forward** in Kansas raised $1m in the second tranche of a series A round, to fund development of its *AV Fistula Eligibility system*, a small minimally invasive blood pump designed to temporarily stimulate flow-mediated vein dilation to help the creation of AV fistula and AV graft access sites. **Laminate Medical Technologies**, in Tel Aviv, Israel, raised $8m in a series B round to fund commercialization of its CE-marked device *VasQ*. VasQ is shaped like a sleeve to go over the fistula and reduce fistula failure. It helps to regulate flow around the fistula and reinforce and shield the vein against high pressure, wall tension and flow levels.

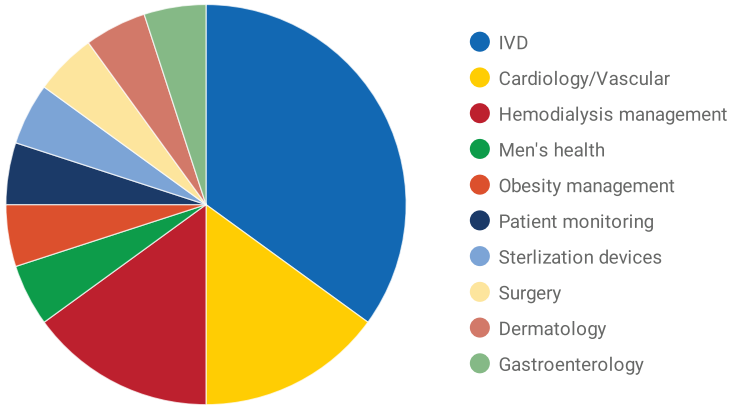
The three investments within the hemodialysis management space in February were on par with the three financing deals in February in the cardiology/vascular space. IVD-related companies were again the most popular among investors last month, with a tally of seven investments. (See Figure 2.)

Looking ahead, March has already had a major jumpstart with a whopping $900m investment round raised by Grail, the spin-out of next-generation sequencing firm Illumina. The funds make up the first tranche of what Grail hopes to be a $1bn series B round, and the company plans to raise the remainder before the end of the month. The firm has got several big names in pharma, tech and medtech as strategic investors; it plans to use the funds to advance development of its pan-cancer test, a single blood test capable of screening asymptomatic patients for cancer. *(Also see "Big Pharma Helps Pour $900m Into Grail" - Medtech Insight, 1 Mar, 2017.)*.

Should Grail complete its $1bn series B as planned, this marks not only the first fundraising of this magnitude but it would also more than mitigate the slow start to VC activity levels so far and give a tremendous boost to 2017's total deal value.

FIGURE 2

No. of venture financing deals by product/therapy sector, Feb 2017



Source: Medtech Insight VC deal tracker

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Published online 03/07/17

First Robotic System To Drill Into Dental Sector Gets US Green Light

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Neocis Inc., based in Miami, Florida, is hoping to cement a strong bond with dental surgeons with the introduction of its newly US FDA-cleared robotic system, said to be the first of its kind to be used in dental implantation procedures to offer physical and visual guidance to the surgeon.

The company announced Mar. 2 that it had received 510(k) clearance for its *Yomi* robotic guidance system. Veteran surgical robotics engineer and CEO of Neocis Alon Mozes, said the system fills an unmet need in the fast-growing dental implant market for robotic surgery, which he valued at an estimated $2bn for the US and at $5bn worldwide. (See Fig. 1)

The Yomi system, which incorporates haptic robotic technology, includes software that assists surgeons with preoperative planning and navigational guidance of surgical instruments during surgery.

"The surgeon can plan everything ahead (using cone-beam computed tomography (CBCT) imaging and planning software), and when it's time for surgery, the surgeon can use the drill and hold it like they normally would, but when they are getting ready to drill, the guidance arm makes sure that they drill with the proper angle, proper position and proper depth according to the plan they had in advance," explained Mozes. The procedure is being tracked in real time on a computer screen, providing the surgeon with clear visualization of the surgical site. (See Video 1).

Mozes likened the system to a "GPS system on the screen" that updates in real time. What makes Yomi different from a pre-manufactured plastic surgical guide -- which offers physical guidance according to a preset plan, but no visual guidance – is that it is flexible enough to divert from the preoperative plan during surgery.

"So if a surgeon is in the middle of surgery and changes his mind about the location of the implant or doesn't like the bone density, all they have to do is update the plan and the system will guide them to the new location right away," Mozes said. "[On the other hand,] the plastic drill guide is pre-manufactured ahead of time, so if surgeons don't like where the drill is being placed, they either need to stick with it or proceed free-hand."

He added, "With our system, the precision, accuracy, reliability and ability to change their plan are a big clinical advantage for the surgeon."

Mozes expects the biggest demand for Yomi will come from "high-volume specialists who really care about providing the highest standard of care."

The CEO, who himself helped develop software for **MAKO Surgical Corp.**'s *Rio system* for orthopedic robotics surgery, declined to say how much the Yomi system will cost, but said that the team's collective experience in developing robotic systems allows Neocis to make the robotic system at a relatively low cost, which, in turn, will make it "affordable" for the dental industry.

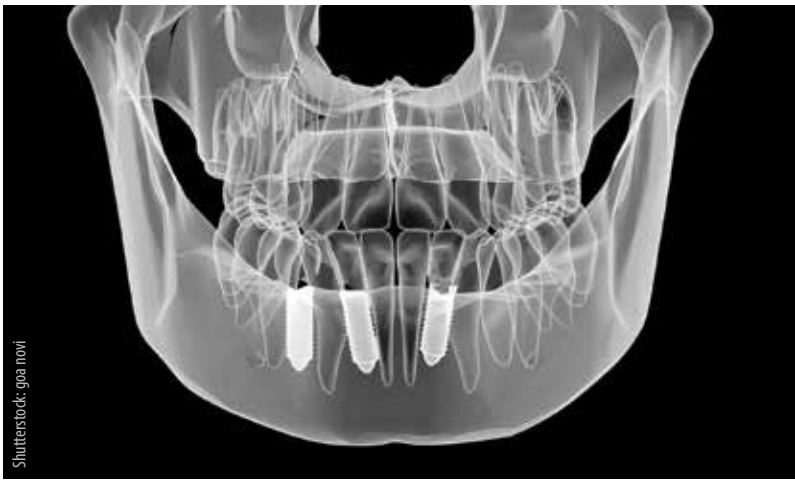
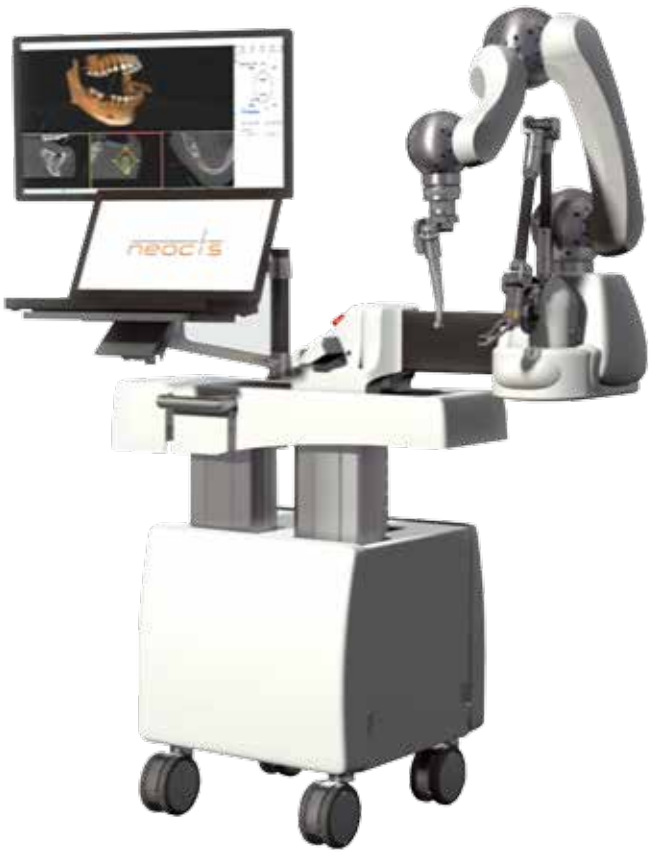


FIG. 1

Neocis Inc. Yomi robotic system



Source: Neocis Inc.

GOING DIRECT

Dental implant surgery remains the standard of care for missing teeth, with more than four million implants being placed in the US every year by 15,000 dental specialists and nearly 150,000 general practice physicians, according to Neocis.

Mozes takes pride in the fact that Neocis is the first to bring to market a robotic system for dentistry. "No one else has a robotic system in the dental industry," said Mozes. "And while it's certainly a different industry than orthopedics, robotic surgery is something we have great experience in, and we wanted to extend the use of robotic surgery to other markets. We identified the dental implant market as large and growing, and it lends itself nicely to robotic surgery. In many other robotic surgery markets, there is a lot of hassle with surgeons needing to go through setting up and using a robotic system. [In dentistry,] teeth are exposed and rigid, which lends itself to patient tracking and drilling into the bone, which makes it much easier to work into the surgeons' workflow."

Asked about Neocis' commercialization plans, Mozes told *Medtech Insight* that the company will manufacture the system in-house and rely on its own marketing and sales team to bring Yomi to oral surgeons, periodontists, prosthodontists and dental specialists focusing on dental implant procedures.

Neocis was co-founded in 2012 by Mozes and fellow Mako Surgical alumnus Juan Salcedo. Salcedo was the principal robotic design engineer and main designer in Mako 's first- and second-generation robotic systems. The company raised its seed funding from industry heavyweight Fred Moll, who founded **Intuitive Surgical Inc.** Other investors include San Francisco-based investment firm Mithril Capital Management LLC, as well as Florida-based investors and former Mako employees, Mozes said.

TOO DEAR FOR DENTISTRY?

Stephen Munroe, a periodontist and owner of Hillcrest Periodontics, based in San Diego, California, agreed with Mozes that the robotic technology offers advantages. But he speculated that cost will likely put it out of reach for many oral surgeons.

"It could enhance accuracy, and, potentially, it could standardize an experience for a more predictable outcome," Munroe told *Medtech Insight*. "The biggest issue in dentistry is that new technologies are expensive and typically the biggest challenge for dentists is to maintain a standardized overhead cost."

Munroe said he uses CBCT imaging in his office -- a technology that can cost between $100,000-$200,000, plus a surgical navigation system, which runs between $20,000-$30,000 – to perform dental implant surgeries.

But Mozes argues that much of these costs above won't apply to using his system.

"We're replacing the need for the navigation system, which only offers visual guidance, and we replace the need for the plastic surgical guide, which only offers physical guidance and creates clinical challenges," Mozes explained.

John Patterson, a general dentist and owner of Patterson Dental in Phoenix, Arizona, said by looking at Neocis' YouTube video of the Yomi system, he agreed with Mozes that the robotic system looks like an enhancement to using a surgical guide, which he uses in his practice.

"It appears that the system will eliminate excessive vibration, leading to less bone trauma, less swelling and pain," Patterson said.

Mozes argues that navigation systems on the market today – such as Lansdale, PA-based company **X-Nav Technologies Inc.'s***X-Guide Dynamic 3D Navigation system* and Canadian-based **ClaroNav's***Navident* system -- only provide visual guidance, forcing the doctors to look at a screen for guidance. By comparison, Yomi offers surgeons both visual and physical guidance and the flexibility to change the preset plan during surgery, he added.

Asked about the company's near-term and long-term plans, Mozes said the immediate focus is to find high-volume specialists who are interested in cutting-edge technology and looking to differentiate their practice. Long-term, he said, he's entertaining multiple opportunities.

"We can expand it into the health care industry and within the dental industry," he said.

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US APPROVALS ANALYSIS:

Strong Month For IVD *De Novos* In February

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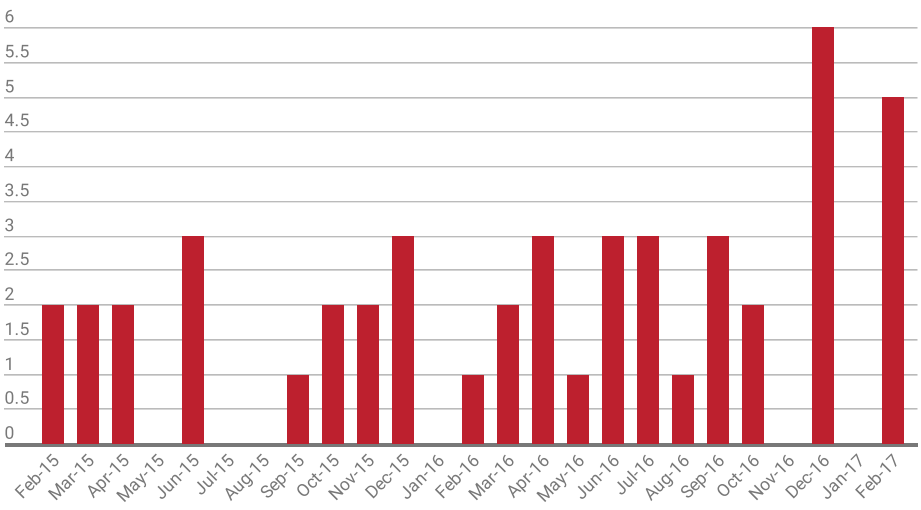
The FDA granted market go-ahead for five devices via the *de novo* classification process in February. That is well above the 1.8-per-month two-year average for *de novos*, a regulatory route for moderate-risk, novel devices.

The *de novo* classification process has gained popularity in recent years, in particular, since Congress allowed companies in 2013 to directly submit an application under the program rather than have to first pursue a 510(k) that is fated to fail due to the lack of a market predicate. *(Also see "Successful De Novo Petitions Double With Advent Of Direct Route" - Medtech Insight, 28 Oct, 2014.)* Nonetheless, five *de novos* in one month is noteworthy. In the past two years, there has only be one other month with a larger total – six were granted in December 2016. For comparison, no *de novos* were awarded in January of this year and only one was granted in

FIGURE 1

De Novo Classifications: Two-Year Trend



Source: Medtech Insight Approvals Tracker

FIGURE 2

Novel Device, Indication Approvals: February 2017

DEVICE NAME	COMPANY	PATHWAY	CLINICAL SPECIALTY	DECISION DATE
Accelerate Pheno system Accelerate Phenotest BC Kit	Accelerate Diagnotics	De Novo	Microbiology	02/23/17
Companion	LGCH INC	De Novo	Neurology	02/16/17
FilmArray NGDS Warrior Panel	BioFire Defense LLC	De Novo	Microbiology	02/14/17
Variola virus Real-Time PCR Assay	Centers For Disease Control And Prevention (Cdc)	De Novo	Microbiology	02/06/17
SEEKER System	Baebies Inc.	De Novo	Clinical Chemistry	02/03/17
Melody Transcatheter Pulmonary Valve Ensemble Transcatheter Valve Delivery System And Ensemble Ii Transcatheter Valve D	Medtronic Inc.	Panel-Track PMA Supplement	Cardiovascular	02/24/17
Propel Contour Sinus Implant	Intersect Ent	Panel-Track PMA Supplement	Ear Nose & Throat	02/23/17
Lutonix 035 Drug Coated Balloon PTA Catheter	LUTONIX	Panel-Track PMA Supplement	Cardiovascular	02/07/17
Tryton Side Branch Stent	Tryton Medical Inc.	Original PMA	Cardiovascular	02/21/17
Cobra Pzf Nanocoated Coronary Stent System	Celonova Biosciences Inc.	Original PMA	Cardiovascular	02/21/17
Pro-Kinetic Energy Cobalt Chromium (Cocr) Coronary Stent System	Biotronik Inc.	Original PMA	Cardiovascular	02/14/17
Aptima Hcv Quant Dx Assay	HOLOGIC INC.	Original PMA	Microbiology	02/13/17

Source: Medtech Insight Approvals Tracker

February 2016. (See Figure 1, "*De Novo* Classifications: Two-Year Trend.")

IVD ACTION

Four of the five devices granted *de novos* last month were *in vitro* diagnostic products, and three of those target infectious diseases. Among them are **Accelerate Diagnostics Inc.**'s *Accelerate Pheno* system and *Accelerate PhenoTest BC* kit, designed to identify and test for antibiotic susceptibility of pathogens directly from positive blood culture samples. The system delivers results up to 40 hours faster than conventional methods for specific pathogenic bacteria commonly associated with bacteremia, the leading cause of sepsis, according to Accelerate.

Also, **BioFire Diagnostics Inc.**, a **BioMerieux Inc.** subsidiary, gained FDA go-ahead for its *FilmArray NGDS Warrior Panel*, a point-of-care system that tests for biological warfare agents and was developed with the US military. Also in the biodefense category, FDA granted a *de novo* to a US Centers for Disease Control and Prevention rapid smallpox assay last month.

Early last month, FDA also permitted marketing of the *Seeker* System, the first newborn screening assay for four, rare Lysosomal Storage Disorders (LSDs) – Mucopolysaccharidosis Type I (MPS I), Pompe, Gaucher and Fabry. *(Also see "FDA Panel Supports Baebies' Seeker Newborn Screen Test" - Medtech Insight, 10 Aug, 2016.)*

The fifth *de novo* from February, although classified as a neurology device, also fits under the diagnostics/monitoring rubric. It's a "physiological signal-based seizure monitoring system" called *Companion*,developed by LGCH Inc.

High-risk novel device approvals also had a healthy month in February, with four original PMA approvals; that is about on-par with the two-year monthly average in this category. Cardiovascular devices received the most attention here, with approvals of coronary stents from **Tryton Medical Inc.**(*Tryton Side Branch Stent*); **CeloNova BioSciences Inc.** (*Cobra PzF Nano-Coated* stent); and **Biotronik SE & Co. KG** (*Pro-Kinetic Energy* cobalt-chromium stent).

SUPPLEMENTS, 510(K)S MAINTAIN PACE

FDA also kept close to monthly averages for the other pre-market submission pathways in February. The agency approved 81 PMA supplements, including panel-track supplements and excluding 30-day notices, up from a below-average 40 approvals in January. And, as for the most-used US pre-market pathway, there were 244 510(k) clearances in February, up from 220 cleared last month and 226 in February 2016.

One noteworthy 510(k) clearance from last month was **Velano Vascular Inc.**'s for *Pivo* needle-free vascular access device, which is a single-use, disposable device that is intended, in particular, to help hospitals address "Difficult Venous Access" patients, according to the company.

Also, FDA cleared **BTG PLC**'s *EKOS Control Unit 4.0*, an ultrasonic device system that uses acoustic pulses to dissolve blood clots and restore blood flow in patients with pulmonary embolism, deep vein thrombosis, and peripheral arterial occlusions.

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OUS APPROVALS ANALYSIS:

Medtronic Records Another Stack Of Overseas Approvals

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February 2017 was another big month for **Medtronic PLC** in securing approvals outside the US, with seven CE marks in Europe plus one approval in Japan and one in Canada.

The 22 CE marks and six non-European approvals in February is eight more than the total number of non-US approvals on *Medtech Insight's* Approvals Tracker the previous month of January, three more than February 2016, and the highest number for any month since the 31 recorded in June.

Medtronic's nine approvals represented almost a third of the 28 non-US approvals recorded on the Approvals Tracker and nine of the ten cardiovascular device approvals during February. (See Figure 1.)

On Feb. 13, Medtronic announced the CE mark and US FDA 510(k)-clearance of the *DxTerity* diagnostic angiography catheter line plus several new interventional devices designed specifically for transradial – through the radial artery in the arm rather than the femoral artery in the patient's leg – access. This included the *DxTerity TRA*, InTRAkit access kit, and TRAcelet compression device. DxTerity and DxTerity TRA are both angiography catheters used to determine if a patient with suspected coronary disease needs revascularization, but the DxTerity TRA is designed specifically for transradial access. It allows diagnostic imaging of both coronary arteries without catheter exchange.

The InTRAkit access kit provides ergonomic needles that offer excellent flashback visualization during transradial interventions, atraumatic miniguidewires, as well as tapered introducer sheaths that provide kink resistance, and enhanced lubricity for easy insertion. TRAcelet is designed specifically for closing the radial access site.

The popularity of the transradial approach over the traditional transfemoral access approach for percutaneous coronary interventions has grown rapidly in recent years – especially among some high-volume operators in Europe, Japan, and Canada – with the accumulation of clinical data showing it is usually less traumatic for the patient. A 2016 metaanalysis by Giuseppe Ferrante, of Humanitas Clinical and Research Center in Milan, and colleagues showed that, compared with femoral access intervetntions, radial access PCI reduces mortality and improves safety, with re-

ductions in major bleeding and vascular complications across the whole spectrum of patients with coronary artery disease.

To support its line of transradial access products, Medtronic recently launched the Transradial Arc Curriculum education and training solution for physicians, staff and administrators "to ensure successful adoption of the transradial approach from access to patent hemostasis."

Also in February, Medtronic announced the CE mark for a whole suite of new magnetic resonance imaging-compatible quadripolar cardiac resynchronization therapy pacemakers that it will launch in Europe in March. The new devices, which are compatible with 1.5 or 3 Tesla MRI, includes the *PerceptaQuad* CRT-P *MRISureScan*, *SerenaQuad* CRT-P MRI SureScan, and *SolaraQuad* CRT-P MRI SureScan.

Medtronic has taken market-share from **Boston Scientific Corp.** and **St. Jude Medical Inc.** in recent years because it had magnetic resonance imaging-compatible versions of its devices in markets where its rivals did not. But in 2016, the company lost share of the CRT-P market because it did not have a quadripolar CRT-P to go along with its "quad" CRT-D devices, so this launch will help remedy that disadvantage. *(Also see "Medtronic Misses Mid-Year Mark With 'Disappointing' 3% Growth" - Medtech Insight, 23 Nov, 2016.)*

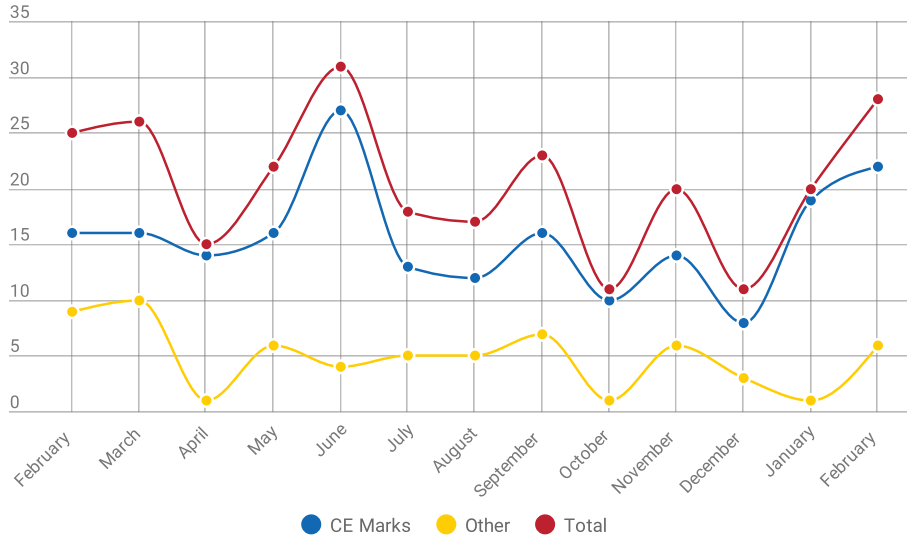
Also, on Feb. 17, Medtronic announced Japanese regulatory approval for its *Micra* transcatheter pacemaker, based on data from the 744-patient Medtronic Micra TPS Global Clinical Trial.

In most months, the biggest category of non-US approvals is in-vitro diagnostics, but in February, IVDs were the third biggest category with five approvals. Mostly because of Medtronic's contribution, cardiovascular was the biggest device category in February with 10. Orthopedics was the second-largest with nine approvals, mostly because of **Spineway**'s seven, including five spine repair devices. (See Figure 2.)

The French company announced that all of its products now have a CE mark, including the *Twin Peaks* lumbar interbody fusion device, the *Mont Blanc* posterior thoracolumbar system for disc and spine repair, the *Kili* anterior lumbar interbody fusion cage, the *Blue Mountain* anterior cervical interbody fusion plate, and the *Ayers Rock* anterior cervical interbody fusion cage. The company also announced CE marks for *Sonora* and *Neve* bone substitutes for treating bone fractures and mechanical defects.

FIGURE 1

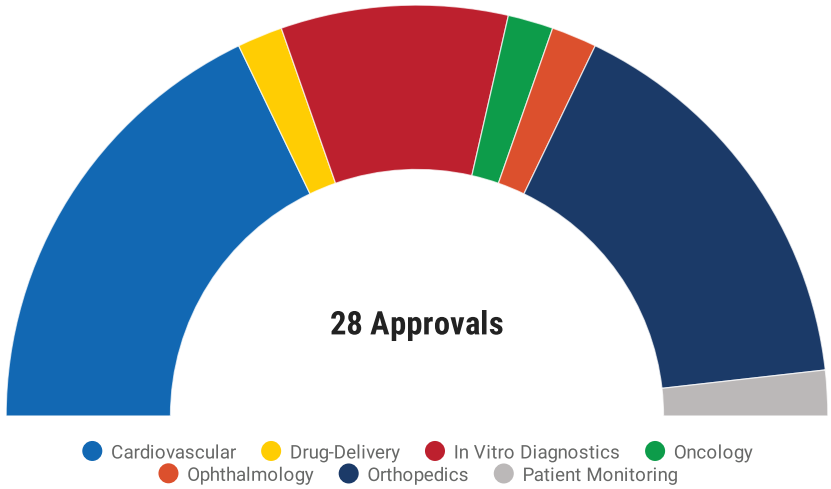
Non-US Approvals, February 2016 - February 2017



SOURCE: Medtech Insight's Approvals Tracker

FIGURE 2

February Non-US Approvals By Category



SOURCE: Medtech Insight's Approvals Tracker

February's list of IVD approvals includes two from medtech and pharma giant **Abbott Laboratories Inc.**On Feb. 17, Abbott announced it had CE marked a polymerase chain reaction test for varicella zoster (chickenpox, shingles) DNA to be run on **Applied Biosystems Inc.**'s *ABI Prism 7000*, *770*, and *7900HT* sequence detection system. On Feb. 21, Abbott said it CE marked its *RealTime* high-risk human papillomavirus test, which can detect 14 high-risk HPV genotypes with simultaneous identification of HPV 16 and 18, according to the company.

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