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Increasingly Less-Invasive Diagnostic Techs To Disrupt Interventional Cardio Market

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The global market for diagnostic and guided interventional cardiology products is forecast to grow from $3.5bn in 2016 to $4.8bn by 2021, at a compound annual growth rate (CAGR) of 6.4%. (See Figure 1.)

This is driven in large part by the continued global burden of cardiovascular disease (CVD), which is responsible for over 17 million deaths annually. The growing elderly demographic, increasing prevalence of risk factors, such as obesity and diabetes, in much of the developed world and continuing high rates of cigarette smoking in parts of the developing world continue to give rise to all types of CVD. This, in turn, translates into a steady flow of CVD patients requiring interventional cardiology devices to manage their condition. *(Also see "Relentless Rise Of Transcatheter Tech: Heart Valve Repair Turns Back On Open Surgery" - Medtech Insight, 24 Jul, 2017.)*

According to *Meddevicetracker*'s "Diagnostic and Guided Interventional Cardiology Products Market" report, transcatheter angiography systems -- which comprise sales of high-cost cardiac X-ray machines and angiography catheters and accessories -- accounted for the lion's share of 59% of total product sales.

While transcatheter angiography systems are considered the "gold standard technique in diagnosing and guiding interventional cardiology procedures," this product segment is expected to see the slowest growth, expanding at a CAGR of 3.1%, from $2.1bn in 2016 to $2.5bn by 2021.

Meanwhile, sales of intravascular ultrasound (IVUS) devices accounted for 14% of the total diagnostic and guided interventional cardiology products market, ranking it the second largest segment. IVUS product sales are expected to grow modestly from $491.4m in 2016 to $664.4m by 2021, a CAGR of 6.2%.

The third largest segment, in terms of product sales, were guide wire-based intravascular stenosis assessment or fractional flow reserve (FFR) devices with an 11% mar-

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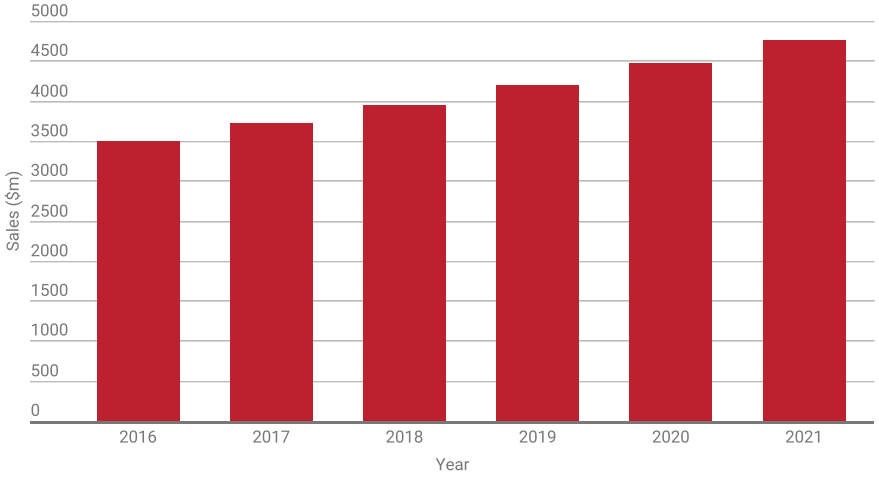
FIGURE 1

Global Market Forecast For Diagnostic And Guided Interventional Cardiology Products For 2016-2021



Source: "Diagnostic and Guided Interventional Cardiology Product Market," Meddevicetracker

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

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official public reaction to the first draft implementing acts linked to the new EU Medical Device and IVD Regulations, background discussion suggests considerable anger and frustration – in particular, with a document that sets out codes for notified body designation for IVD oversight.

COMPANIES

R&D

START-UP SPOTLIGHT

NuVasive, Alphatec At Odds Over Exec Job Change

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A former **NuVasive Inc.** executive's move to smaller spine-device competitor **Alphatec Holdings Inc.** has sparked a lawsuit, with Nuvasive claiming former president and COO Patrick Miles breached his contract and defrauded his former employer. Alphatec, however, said the allegations were false and decried the suit as a "PR stunt."

The complaint was filed Oct. 10 in Delaware Chancery Court.

In January 2016, a financial services company asked NuVasive whether they might be interested in purchasing spinal-fusion company Alphatec. The company passed on the bid after Miles advised that the acquisition was "a waste of time" and that Alphatec had an "aged, undifferentiated portfolio," NuVasive says in its complaint.

Miles then joined NuVasive's board in August 2016. A few weeks later, he told the company that he'd received a job offer from Alphatec, but said he "did not want the huge workload associated with a high-level management position with NuVasive or Alphatec." In response, NuVasive made Miles a vice chairman with a compensation package that included an annual salary of $500,000 as well as $3.7m in equity. The company also negotiated non-compete agreements that would blocked Miles from seeking work in the medtech industry, hiring former NuVasive empoyees, or soliciting the firm's clients for one year after leaving, the complaint states.

But Miles bought $500,000 worth of Alphatec stock in March 2017 – a violation of its conflicts-of-interest policy, Nuvasive said. He also reportedly "disparaged NuVasive and key members of its management to critical NuVasive customers, medical partners, and employees, in order to lay the groundwork to transition them to Alphatec."

Miles was still officially a NuVasive employee and board member when he reached an agreement to serve as Alphatec's executive chairman. His compensation for the role included one million shares of Alphatec stock, worth $3.2 million. Miles further agreed to invest $2.9 million for an additional 1.3 million stock shares, and got permission to later purchase another 1.3 million shares. NuVasive estimates that, taken together, the deals could see him own up to 23% of Alphatec's outstanding stock.

Nuvasive alleges that Miles tried to recruit more than two dozen current and former customers and employees, and one has already resigned to join Alphatec. He also spoke to distributors, with one distributor employee reportedly following Miles to Alphatec.

On Sunday, Oct. 1, Miles resigned from his job at NuVasive and told the company he would join Alphatec the next day. He also stated that he didn't believe his noncompete agreements were enforceable.

The decision to sue "was not taken lightly, particularly given Mr. Miles' history with NuVasive," the company said in a statement. "Yet it is this history and Mr. Miles' intimate knowledge of the company and our proprietary information that makes his breach of fiduciary duties and contractual obligations so egregious and this litigation necessary."

Alphatec, meanwhile, said in a statement that the lawsuit is "fictional" and designed "to inflict maximum damage to the public reputations of both Mr. Miles and Alphatec."

"The allegations made by NuVasive against me are clearly false, and typical of a management team reacting to mass departures of key, spine-experienced executives," Miles said. He plans to file a response to the complaint, and Alphatec has pledged its support.

The lawsuit alleges breach of contract, breach of fiduciary duty, fraud, and unfair competition, among other charges. NuVasive is asking for compensatory and punitive damages, a repayment of Miles' salary, and court costs.

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Investigator Horror Stories 2: More Terrifying Tales Of FDA Inspections Gone Bad – And How They Were Fixed

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This Halloween, trick-or-treaters might not be the only ones wearing a disguise. When you're on the manufacturing floor at your medical device company, take a sharp look at the person standing next to you – he or she could be an imposter from US FDA.

That's what happened to a maker of combination products several years ago at a facility in Brooklyn, NY, says Francis Blacha, global quality leader for devices for **Eli Lilly & Co.**, who told *Medtech Insight* that an agency investigator spent days trying to infiltrate the company (which he did not identify) in a bizarre, desperate bid to meet the CEO.

Shutterstock: Andrea Danti

"FDA is required to, when they do a notification of inspection, issue a Form-482. Investigators must give the form to the most senior person at the firm, which is typically the CEO. A lot of investigators take that task extremely seriously," Blacha said in an Oct. 11 interview.

And at the Brooklyn firm, "the investigator took that on as a personal challenge," he said. "I don't know whether he had the firm under surveillance or not, but he suspected that that the company CEO was there because in the parking lot, the CEO had a dedicated spot, and he could see that a car was parked there."

"The firm didn't have appropriate security at this facility. If this disguised investigator could get in, what would prevent somebody else with more nefarious intentions from getting in?" Eli Lilly's Francis Blacha says.

Despite the circumstantial evidence, company employees told the investigator that the CEO was not in the facility. That's when he took matters into his own hands.

"What the investigator began doing was, he would come to the plant disguised as an employee. He would wear a black leather jacket and sunglasses. He had facial hair. He'd ride up to the facility on a Harley motorcycle instead of in a government car. He would park the Harley in the employee parking lot, surround himself with actual employees, and then try to make it through the facility to the CEO's office to present the 482 to him."

The investigator – who didn't produce credentials or a government-issued badge – wore the disguise on three separate occasions until he was caught. "He never quite made it to the CEO's office, but he got very close," Blacha said. Eventually, the investigator gave up and handed the notice of inspection to the CEO's subordinate.

"The investigator finally came clean and said, 'Hey, you know what? I've got to get on with this inspection, so I'll give [the FDA-482] to whoever you tell me is the senior person at the firm,'" Blacha said. For whatever reason, the manufacturer never reported the rogue investigator to the agency, but it did double security efforts following the unusual incident.

"The firm didn't have appropriate security at this facility. If this disguised investigator could get in, what would prevent somebody else with more nefarious intentions from getting in? Clearly they didn't have appropriate security measures if someone was getting that far into their facility," Blacha said.

"I don't know if the investigator was proving a point that the firm had a lack of security, or he simply knew that the CEO was there," he said. "But it was very strange for him to not use a government car, to drive up on a motorcycle and to try to blend in with the crowd to be able to navigate his way through the facility undetected."

Blacha suggested that having procedures and policies in place to handle unannounced inspections could help diffuse such sticky situations.

"Clearly, when somebody shows up and presents their credentials – and even if they don't – you should ask them, 'Please identify yourself,'" he said. "You have to make sure that you have the appropriate procedures in place and a list of appropriate contacts. And don't make investigators wait forever."

While few and far between, stories of FDA inspections gone horribly awry aren't unique. In fact, last year's most-read *Medtech Insight* article detailed how an investigator followed a device firm's employee into a restroom to stop her from using a cell phone, while another attempted to fix a manufacturer's rooftop HVAC unit. *(Also see "Investigator Horror Stories: Industry Insiders Tell Of FDA Inspectional Nightmares – And How Device Firms Handled Them" - Medtech Insight, 7 Jun, 2016.)*

In this second edition of "Investigator Horror Stories," Blacha and Ricki Chase – a former FDA investigations branch director – tell a trio of real-world stories of other troublesome inspections, and offer solutions on how firms should respond if they encounter an auditor who engages in strange or unexpected behavior.

THE CURIOUS CASE OF THE CRYING INVESTIGATOR

During her 16 years at FDA – she left in 2016 – Chase witnessed peculiar behavior from agency investigators, she said in a February episode of Compliance 360°, a podcast series from *Medtech Insight* on US FDA compliance and enforcement issues.

"Throughout my years, I had numerous opportunities to train and to audit the investigators, and noted attitudes and behaviors that could've been perceived by our partners in industry as aggressive, difficult, inappropriate, and even weird. This has included … crying uncontrollably without explanation," said Chase, who was also an investigator, medical device specialist and supervisory investigator at the agency.

In an Oct. 19 follow-up interview, she told the full story of the weeping investigator.

"There was an investigator that I was a colleague with, and I don't know why, but for some reason, any time she was stressed, she cried. And being an FDA investigator can be very stressful," said Chase, now compliance practice director for Lachman Consultant Services.

"I took her out on investigator training, and in the middle of a conversation with the firm regarding some SOP [standard operating procedure] that seemed very insignificant at the time, she just started crying. I'm sitting there thinking, 'Why is this person crying?'"

The quality assurance official at the firm that was being inspected – who also served as the lead for the audit – was taken aback as the investigator-in-training continued to cry uncontrollably.

"I mean, it's very uncomfortable sitting there watching somebody cry with no explanation while they're reading your SOP," Chase said.

"The first thing the QA lead did was get up and get a box of Kleenex and slide it across the table in a very kind of precarious, 'OK, here, do you want some Kleenex?' kind of way," Chase added. "And then, after she started dabbing her face, she began crying even more. So, I said to the lead, 'I think we're going to need to

call a timeout. If you could just give us a few minutes.'

"The only thing the person at the firm could think to say was, 'I didn't think our SOP was that bad,' to which I immediately started laughing, which did not help the situation at all. She did not come back the next day, for obvious reasons – she was taken off the inspection."

When Chase told her supervisor at FDA what transpired, "he thought I was lying," she said.

The supervisor then accompanied the weeping investigator on an inspection. To his surprise, "the investigator started crying at the close-out meeting," Chase said. "She made it through the entire inspection, but when the FDA-483 [inspection observation form] was being issued to the firm and she had to discuss the 483 issues, she cried." *(Also see "Compliance 360° Part 2: Getting The Most Out Of Inspection Close-Out Meetings" - Medtech Insight, 13 Feb, 2017.)*

The investigator was not terminated from the agency, though. "I think she knew that she was short-lived for being an investigator, so she went back to working in FDA's lab, which I think she was probably better suited for, where she didn't really have to have a whole lot of human interaction," Chase said.

How should a similar situation be handled?

"If an investigator is upset, obviously, the appropriate thing to do would be to be sympathetic and say, 'I'm very sorry, I can see you're upset. Is there something I can do to help you?' And if they say no and they continue to go on, I think that – unless the investigator pulls it together – the firm has the right to question where that person's mind really is," Chase said.

"The last thing you want is an investigator who is emotionally distraught about something else, or, for whatever reason, can't manage what's going on. They're certainly not going to be focused on what you're doing, and they're certainly not in a position, I wouldn't think, to be making a good decision regarding your compliance status," she said.

If the situation continues, Chase recommends that firms ask to end the inspection day.

"The firm could say, 'There's something clearly going on, and I feel uncomfortable that we're not going to make good headway today working together. Perhaps you would like to end the day. Perhaps you'd like to come back tomorrow,'" she suggested.

"If they continue to say no, then I would definitely call their division office," Chase said. "You should call and say, 'I need to speak to whoever's the manager of this individual. They're in my firm right now, and I feel like we have a little bit of a situation that is timely and we need to discuss it.' And the firm doesn't need to be rude about it, but I think they need to say, 'You know, I'm very concerned about this investigator. They're sitting in my conference room weeping, and they can't seem to pull it together and they don't seem to want to come back tomorrow, so how would you like to proceed on this?'"

Another option that device-makers have is to call the division director.

"Regardless of what program the division director works in, the director will know exactly how to get to the right person probably faster than anybody else," Chase said. "It's always OK to speak to the division director, and even if it's not their program area, they have a responsibility, if that's going on, to do something about it immediately."

THE INVESTIGATOR WHO WANTED TO GO HIGH

Eli Lilly's Blacha was involved in an FDA inspection several years ago at an unnamed firm, during which time the investigator was laser-focused on looking at nonconforming components that were stored about 20 feet off the ground in a quarantined section of a warehouse.

"The QA people were there to raise the forklift, pick up the pallet and bring it down to the floor so the investigator could see it. But the investigator didn't want to do that. Rather, he wanted to go up onto the pallet himself," Blacha said.

The firm didn't want to do something so dangerous – yet it did anyway, but only to a certain height.

"There was a bunch of consultation and stuff like that; finally, the firm agreed to raise the investigator up to only about 8 feet so he could look at information on the components' pallet tag," Blacha said.

At that point, "the firm said, 'That's all. We're trying to be cooperative as much as possible, but we're only going to bring you up to this height so you can see the pallet tag. If you want to see any more information on the pallet, then we must bring the pallet down to the floor,'" he said.

"After a while, people should say, 'Hey, you know what? This is kind of weird. We may need to talk to somebody else about this,'" Blacha says.

"To this day, I don't know why the investigator would not let them bring the material down to the floor. For some reason, he just wanted to go up and see it for himself," Blacha added. "A lot of times, you might not understand what the reasoning behind something like that is. Maybe he could have been looking at a potential prosecution down the line. But I think after a while, people should say, 'Hey, you know what? This is kind of weird. We may need to talk to somebody else about this.'"

How should a similar situation be handled?

Again, it's best for device-makers to have well-defined policies and procedures on how to handle inspections, and to lay out boundaries for investigators, Blacha said.

Firms need to let investigators know that some areas and activities are off-limits because the auditors could put themselves in physical danger.

Manufacturers "should have an area specifically for receiving and inspecting components, and if an investigator wants to see those, then the firm should bring that material down to that area," Blacha said.

THE SECRET OF THE HIDDEN VOICE RECORDER

When an FDA investigator was caught consulting for industry and falsifying inspection reports, his superiors conducted an investigation that led to a shocking discovery, consultant Chase recounted.

"Not only was this investigator doing consulting work for firms he was personally inspecting, but he was trying to play 'undercover cop' too, trying to catch a company lying after officials there complained that he was too aggressive," she said.

In an effort to secretly record conversations that happened at the firm, the investigator hollowed out a hardback notebook and placed a voice recorder inside.

"He recorded everything that the company was saying, particularly when he wasn't in the room," Chase said. "When he was out doing the inspection on the floor and the quality people were left in a conference room discussing the inspection, he was recording what was going on. He was a real interesting piece of work."

An FDA administrator who investigated the crooked auditor's work found the carved-out notebook while poring over journals in the man's desk.

"One of the things you have to do to verify if somebody actually inspected a firm is to get their investigative journals. There must be an investigative journal entry for every inspection," Chase said.

When the notebook was discovered, the recorder was found not long after, which included detailed conversations at the company. Soon after, the investigator was fired.

How should a similar situation be handled?

Chase admits that this was an extreme case, and that manufacturers likely won't encounter such deception. But if they do, they should immediately contact FDA.

"You know, people do really weird things, but there's a difference between being weird and doing something illegal, which is what this individual was doing," she said.

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Why Low-Risk And Upclassified Devices Must Heed EU Timeline Warnings

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It's true that many products can continue to be placed on the EU market and put into service after the full-application dates of the new new Medical Device and IVD Regulations in 2020 and 2022, respectively. Although, there are strict rules on which products can benefit from this flexibility.

What is less well publicized is the tight deadlines for devices that do not need the involvement of a notified body and the pressures for all products that are being upclassified under the MDR or IVDR.

Medtech Insight spoke to Bassil Akra, VP of global focus teams (cardiovascular, orthopaedic and clinical) at German notified body TÜV-SÜD Product Service, to explore the matter.

Medtech Insight: Can you explain why class I medical devices are in a different position from all other devices when it comes to compliance with the Medical Devices Regulation (MDR)?

Bassil Akra: Class I medical device manufacturers do not hold a conformity assessment certificate from a notified body and therefore they cannot profit from the grace period laid down in the MDR. These device manufacturers have to show compliance at the latest by the end of the transition period, i.e. May 26, 2020. Moreover, some of these manufacturers may need to upclassify their devices – as is the case for manufacturers of reusable medical devices and substance-based medical devices.

Is this the same situation for class A IVDs under the new IVD Regulation (IVDR)?

Akra: Class A IVDs manufacturers are in the same situation but they have a bit more time based on the different transition period of the two regulations. The date of full application of the IVDR is May 26, 2022. It should be nevertheless recognized that a large number of class A IVDs are upclassified to classes B, C and D and so come under the responsibility of a notified body. This will require better project planning.

How soon can manufacturers of class I medical devices and class A IVDs claim compliance with the new regulations and place a CE mark on their products as such?

Akra: They can start preparing the compliant evidence and technical documentation today, but should communicate with their member states to understand whether the regulatory authorities are accepting registration at the current time. I have asked several authorities about the status and I have been informed that no single manufacturer has sent a request for an MDR/IVDR-compliant device yet.

What happens in the absence of other crucial regulatory structures that are forseen under the regulations? What vital structures are missing?

Akra: The regulations include provisions in case some crucial structures are missing at the time of implementation. These provisions allow the system to run following already available structures. For example, in case no harmonized standards are available at the time of implementation, the old harmonized standards can be used; but the manufacturer has to show how he is using such a standard to fulfill the single general safety and performance requirements of the regulations.

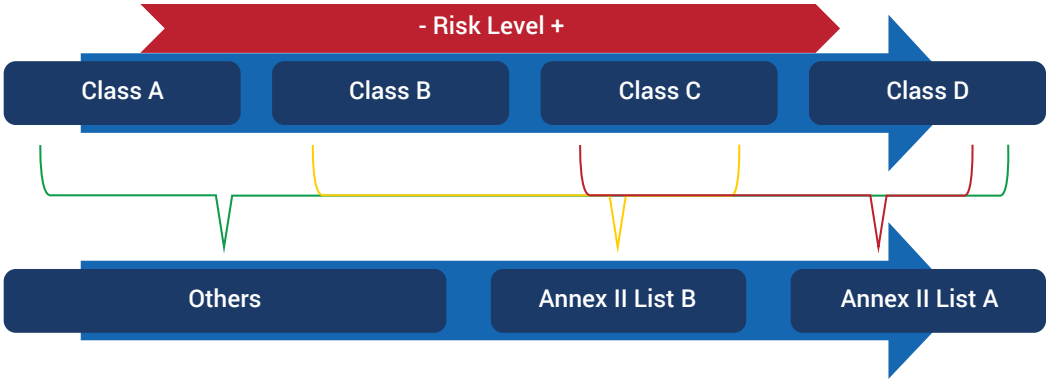
What else do manufacturers of class I medical devices and class A IVDs need to bear in mind?

Akra: They have to start early since their devices may need an upclassification, forcing them to comply in a very limited timeline; notified bodies will not be available for some considerable time due to the delayed designation process and this will shorten the time that is available for their assessments before full application of the regulations.

Moreover, when demonstrating compliance to the new

FIGURE 1

IVDR Classifications



regulations, manufacturers may need to repeat some tests, or to carry out new ones towards claiming compliance.

Which groups of products are being upclassified in the new medical device regulation?

Akra: There are a good number of devices that are being upclassified or that will need to involve a notified body for the first time: Some medical apps will be upclassified up to class III; substance-based medical devices will be upclassified up to class III; and all reusable devices will need a notified body.

In addition, all orthopaedic joints, spinal implants, devices in contact with the heart and devices, including nanomaterials, are being upclassified.

What is the significance of these products being upclassified?

Akra: The new regulation includes provisions which will push, for example, every implant to have different and higher levels of clinical evidence.

Moreover, the applicable annexes for the conformity-assessment process may change too, leading to different expectations of the quality management system and the timelines associated with the level of notified body involvement (e.g., sampling or full review). Companies need to be aware of this and to prepare for it.

For most products, as long as the conformity assessment certificate is still valid, they can continue to be placed on the market and put into service after the date by which the new regulations fully apply, i.e. May 26, 2020 for devices, and May 26, 2022 for IVDs. However, in the case of products that are being upclassified, does the previous certificate become null and void on those dates? Can you explain the rational here and what this means for manufacturers of products that will be upclassified?

Akra: The only devices that will need to upclassify at the end of the transition period and move to the new regulations are devices which are required to have notified body involvement for the first time when they did not in the past.

Moreover, devices which fall under the new scope of the new regulation for the first time, such as most cosmetic devices, must fulfill the requirements by latest at the end of the transition period. The involvement of notified bodies can start when the relevant Common Specification technical document is available allowing notified bodies to understand what should be expected for these kinds of device.

It is worth bearing in mind that for those devices that are still CE-marked under the directives when the date of full application of the regulations arrives, that they will need to comply with post-market surveillance requirements of the new regulation.

How does this apply to IVDs where upclassification is effectively happening on a massive scale?

Akra: All IVDs have to be checked against the new rules (1-7) to see whether they fall under Class B, C or D. In such a case, they would need to be upclassified. Based on my understanding and the information that I am receiving from the market, more than 70% of IVD devices which were put onto market without notified body involvement will need a notified in the future, leading to higher classification. With the new regulation, a small percentage of IVDs will remain in the lowest-risk class compared to the past.

What other factors do companies need to bear in mind if their products are being upclassified?

Akra: Medical device manufacturers must look critically at the timelines related to UDI, and especially to the clinical evidence affected by the higher classification.

They will also have to prepare for the following: General Safety and Performance Requirements; more detailed requirements regarding technical documentation; summary of safety and performance for class C and D IVDs and class III and implantable medical devices; and periodic safety update reports (PSUR) for IVDs and MDs.

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EU Commission May Open Floodgates By Inviting Input On Editorial Errors

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The European Commission is planning to launch an initiative to "correct mistakes of an editorial nature" within the texts of the Medical Devices Regulation (MDR) and IVD Regulation (IVDR) that took effect on May 25 this year.

Industry is not risking any time in preparing responses. Already, Europe's largest medtech industry association, MedTech Europe, put out an invitation via the national industry associations within the EU for stakeholders to communicate the mistakes that they have found. Specifically, industry-members are directed to send details to the email address regulatory@medtecheurope.org, where they will be collated and forwarded to the European Commission.

The Commission will accept comments on any language versions of the MDR and IVDR, which are scheduled to fully apply in the EU in 2020 and 2022, respectively.

While clearly an essential exercise that could improve the clarity of the new regulations, it raises the question of where should industry draw the line in deciding what to put forward. There errors that are strictly editorial in nature, and then there are inconsistencies or ambiguities that run through the texts that make aspects of the regulations very difficult, or even impossible, to implement. To what extent should industry use this exercise to address the latter?

Just to give a few examples of issues that may come up that are not strictly editorial, but have been the focus of attention at recent meetings:

- The need for clarification on Article 61 (61.5 and 61.6) of the MDR concerning claiming equivalence in clinical data: Does it only apply to class III implantable and class IIb devices, or does it apply to all devices?
- Authorized representatives may want clarification in the MDR and IVDR over the term "jointly and severally liable" – no one seems to quite understand what it means in practice. "Recital 35" of the MDR mentions that authorized representatives are jointly and severally liable with the manufacturer and the importer. There may also be calls for clarity over why later in the regulation, in Article 11.5, the text applies the "jointly and severally liable" phrase only with respect to the authorized representative and the manufacturer, but not the importer.
- Authorized representatives may also ask for clarification whether, when it is mentioned that notified bodies should audit critical suppliers, they should be audited by notified bodies (for example in Annex I, Chapter 1, sections 3.3 and 3.4).

When sending their observations, companies are invited to not only cite the original text, but to propose changes in bold/italics. Any problems should be highlighted with words struck through, as appropriate.

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Could First EU Implementing Acts Threaten Timely Designation Of Notified Bodies?

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There has been an angry reaction to one of the first three draft EU implementing acts that were made public in August. The document in question is NBOG WD 2017-3, which – in its current draft form - comprises 100 codes and corresponding types of IVDs devices that can be used to describe a notified body's scope of designation under the new IVD Regulation.

While there have been no public statements, *Medtech Insight* has learned from multiple sources that the draft IVD document is considered overly burdensome by notified bodies seeking designation.

But they are caught between a rock and a hard place; this document is an essential building block that will underpin applications from notified bodies to be designated under the new IVD Regulation.

With the first wave of notified bodies – at least 16-18 – intending to put in their applications in on the first possible day – November 26, 2017 – any challenge and redrafting would hold up the first applications from notified bodies and impact the whole sector's ability to comply in time.

This would mean a delay for manufacturers applying for CE marking under the new regulations and a risk of more companies failing to meet the deadlines for their products. Given the likelihood of bottlenecks at notified bodies even without any delays, this is something that the whole sector will want to avoid.

WHAT IS THE PROBLEM?

The NBOG WD 2017-3 IVD document would effectively mean that the notified

body must spell out quite precisely the type of tests it will assess for its application to be redesignated.

Of note, there are 100 codes in the IVD draft – 29 more than in the parallel draft document for medical devices, NBOG WD 2017-2.

Stakeholders are criticizing the draft IVD codes document for being far too detailed and impractical to implement, *Medtech Insight* understands. There are quite possibly going to be overlaps and challenges to IVD companies of implementing these codes.

Of note, there are 100 codes in the IVD draft implementing act – 29 more than in the parallel draft document for medical devices.

ONGOING DISCUSSIONS

Speaking on behalf of the EU notified body association, TEAM-NB, director Francoise Schlemmer said the association cannot comment any more than to say, "There are ongoing discussions between all stakeholders, especially on the IVDR codes." She also acknowledged that the classification scheme is totally new in the IVD Regulations.

Notified bodies and other relevant stakeholders had previously provided input into the work that was being done on the draft implementing acts, but critics say that the European Commission did not pay sufficient heed to the feedback. Instead, according to sources, the commission believed that the level of requested detail would help authorities better understand the precise designation of the notified body and oversee notified bodies.

The European Commission is understood to be aware of the concerns and considering the matter, although there has been no public comment.

The third implementing act that was issued during the summer also NBOG WD 2017-1, which spells out the documentation that notified bodies will be required to submit in an application for designation under the new regulations.

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FDA Tracks Critical Device Supply During Puerto Rico Hurricane Recovery

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US FDA is monitoring supplies of about 50 critical medical devices as Puerto Rico continues to recover from Hurricanes Irma and Maria, FDA Commissioner Scott Gottlieb said Oct. 20.

Device manufacturing, along with drug manufacturing, account for a major component of Puerto Rico's economy. The island hosts more than 50 device facilities, employing about 18,000 people, which make more than 1,000 different types of devices ranging from surgical instruments to insulin pumps, Gottlieb said. Just about all the major device companies have facilities on the island, including **Stryker Corp.**, **Johnson & Johnson** and **Medtronic PLC**.

But Gottlieb says FDA is most closely focused on a smaller group of devices deemed critically important to patient care, either because they're life-sustaining or life-supporting or because only one facility makes the device. The agency is working closely with about 10 companies, some that are the sole manufacturer of a device type, to prevent product shortages, he says. The agency says most of the devices it is focusing on are "blood-related."

Like all Puerto Rican businesses, device manufacturers on the island are facing challenges around electricity, connectivity, transportation and clean water. Companies are relying on generator power, which has left many unable to return to pre-hurricane production levels, FDA says. In addition, the local subcontractors who provide device manufacturers with materials such as a product components, tools and industrial gases have their own obstacles and shortages to surmount.

FDA's aid to Puerto Rican device manufacturing plants includes helping the facilities secure fuel and providing logistical support to get critical products on and off the island. The agency is also looking at alternative steps, such as allowing manufacturers to shift production to alternative sites and importing devices form outside the US if necessary. In addition, FDA personnel including Chief Operating Officer James Sigg and Associate Commissioner for Regulatory Affairs Melinda Plaisier visited the island the week of Oct. 16.

"We know it will likely be months before power is fully restored and medical product manufacturing returns to pre-hurricane levels," Gottlieb said. "The FDA is committed to helping restore the medical product manufacturing in Puerto Rico as part of our efforts to protect the health of Americans and help the people of Puerto Rico recover their local economies and livelihoods."

Last month, at AdvaMed's Medtech Conference, Gottlieb advised companies facing

challenges in Puerto Rico to tap multiple government challenges "If I was a company with a critical issue, I would make sure I had that same conversation with as many touchpoints as possible, including with FDA," Gottlieb said. "Don't be shy about that." *(Also see "Gottlieb At The Medtech Conference: US FDA Commissioner Talks About CDRH Innovation, Puerto Rico, LDTs And More" - Medtech Insight, 2 Oct, 2017.)*

MANUFACTURERS REPORT VARYING IMPACT

Public statements show manufacturers on the island experienced varying amounts of damage and impact from the hurricane. **Baxter Corp.**, which lost multiple production days, had to transfer some manufacturing to alternate facilities. As of Oct. 4, the company was rationing shipments of some products made in Puerto Rico, such as small bags of dextrose and saline, to prevent stockpiling. **Zimmer Biomet Holdings Inc.**, meanwhile, said on the same date that its facilities sustained minor damage and were still ramping up production to pre-storm levels. But the company estimated that is inventory levels were sufficient to prevent shortages.

Johnson & Johnson CFO Dominic Caruso said during the firm's Oct. 17 third-quarter earnings call that J&J's six Puerto Rican manufacturing facilities have fared well, "considering the magnitude of the storm." The company's plants were all open, running on generator power and shipping newly manufactured products, he said. And while J&J continues to monitor inventories and prioritize manufacture of essential products worldwide.

"While we cannot rule out the potential for intermittent shortages of certain product formats, many of our products have dual-production sites and backup supply outside of Puerto Rico to help meet demand," Caruso said.

"It would appear the hurricane affected different companies different ways going across Puerto Rico, because I've noted that some competitors have indicated more damage or more impact than we've experienced. It took a superhuman effort by a lot of our people to try to address some of that, which we did," **Abbott Laboratories Inc.** CEO Miles White said during the firm's Oct. 18 earnings call. White described the hurricane's impact on Abbott as relatively "modest," and said its plants were running again.

"While we cannot rule out the potential for intermittent shortages of certain product formats, many of our products have dual-production sites and backup supply outside of Puerto Rico to help meet demand," J&J's Dominic Caruso says.

Overall, AdvaMed spokesman Greg Crist said Oct. 20, "Companies are struggling with the same issues and are still working to minimize the impact. IV fluids are in short supply, but [we are] still determining what, if anything, is critically low."

Crist noted that generator maintenance is becoming a bigger issue. "More and more of them are breaking down and multiple companies are challenged with making expedited repairs and flying in technicians and parts," he told *Medtech Insight*. "Another newer issue is the removal of waste oil and filters from these generators. There are regulatory limitations on the amount they are allowed to store on site."

An Oct. 4 letter from AdvaMed to the US Department of Health & Human Services expresses gratitude for the government's efforts, but also highlights to the need for further assistance. Twenty AdvaMed member companies have facilities in Puerto Rico that employ more than 12,000 people. The group says it has been working with federal and local authorities to stabilize facilities. It also says that its members have shipped materials including satellite phones, diesel fuel, water, batteries, medical supplies and generators to the island, but continuing assistance will be needed.

"As the delivery of medical technology plays a vital role in the entire health care ecosystem, we would be grateful for any assistance you could provide in prioritizing these facilities as power and communications are restored," AdvaMed president Scott Whitaker wrote.

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FDA Calling: US Agency Again Asks Companies To Open Doors For Educational Purposes

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US FDA is again asking stakeholders to open their doors to agency officers to observe how the device industry health-care organizations work in the real world. In the latest iteration of the Center for Devices and Radiological Health's Experiential Learning Program (ELP), the agency is specifically looking for its staff to gain more insight in areas including combination products, software and clinical trials.

CDRH is asking companies, academic organizations, clinical facilities, device incubators and accelerators, health insurers, health technology assessment groups, and other stakeholders to volunteer to let the agency use their facilities as training grounds.

"The ELP is intended to provide CDRH staff with an opportunity to understand the policies, laboratory and manufacturing practices, and the challenges addressing patient perspective/input, quality system management, and other challenges that impact the device development life cycle," said CDRH. "These formal training visits are not intended for FDA to inspect, assess, judge, or perform a regulatory function (e.g., compliance inspection), but rather, they are an opportunity to provide CDRH review staff a better understanding of the products they review, how they are developed, the voice of the patient, challenges related to quality systems development and management in the product life cycle, and how medical devices fit into the larger health-care system."

For one requested site visit, CDRH seeks to "understand how firms select new employees, train them to perform the varying complexity levels of service, repair, and maintenance, and how firms validate an employee's abilities to adequately perform such activities."

A Federal Register notice announcing the latest ELP opportunity circulated on Oct. 17, but the latest window for stakeholders to volunteer has actually been open since Sept. 28, and will close on Nov. 1.

Two of the center's ongoing strategic priorities are "partnering with patients" and "promoting a culture of quality and organizational excellence," FDA states in the notice. "For the 2018 ELP, our goal is to specifically understand the perspective of our stakeholders and understand implementation of these topics within their institutions."

The agency listed several broad areas that it would like to better understand. Some particular areas of interest are neuro-oncology medical device combination products, use of radiology reading software and workflow in a variety of clinical environments, and clinical use of computer-aided diagnostic software and workflow.

Another interesting area that FDA wants better understanding of is how employees are trained in the post-market setting.

"The purpose of this ELP would be to understand how firms select new employees, train them to perform the varying complexity levels of service, repair, and maintenance, and how firms validate an employee's abilities to adequately perform such activities," said the agency. "Additionally, FDA would like to understand what competencies are desired for new and existing employees that perform these activities."

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CONTINUED FROM PAGE 1

ket share and $397.8m in sales in 2016. This market segment is expected to reach sales of $644.1m by 2021, a CAGR of 10.1%.

Intracardiac echocardiography (ICE) systems accounted for a 10% total market share in 2016 with $344.4m in sales, but are expected to see double-digit growth with $633.4m in sales by 2021, a CAGR of 13%. This growth is supported by the rising burden of cardiac rhythm disorders and the clinical success that ICE has demonstrated in comparison to transesophageal echocardiography.

OCT systems and robotic-assisted surgical systems accounted for the remaining market share.

That said, OCT systems are expected to see the highest growth over the forecast period with sales growing from $156.3m in 2016 to $296.9m by 2021, a CAGR of 13.7%.

These systems along with ICE and guide wire-based intravascular stenosis assessment will be the key market drivers.

The high demand for these systems is supported by clinical evidence, which translates into cost-savings and improved outcomes that health systems aim for in making the transition to value-based care.

Robotic-assisted systems, meanwhile, are expected to climb from $29.8m in 2016 to $38.6m by 2021, a CAGR of 5.3%. Though this segment is small compared to the other segments, it's considered a highly innovative and promising area pursued by start-ups and big players like **Medtronic PLC**.

GEOGRAPHIC PERSPECTIVE

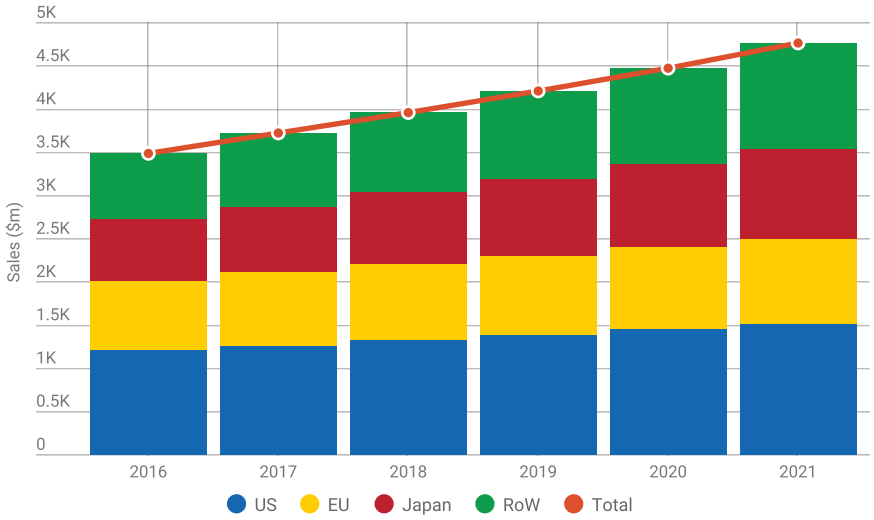
Looking globally, *Meddevicetracker* expects that Japan and the emerging markets, including Brazil, China, India and Russia, will see the strongest growth in product sales during the forecast period, with Japan expanding at a CAGR of 7.7% and emerging markets at 9.8%. (See Figure 2.)

The biggest growth is expected in the emerging markets with sales of diagnostic and guided interventional cardiology products expected to grow from $765.8m to $1.2bn by 2021.

Japan is expected to see the second-largest growth with sales of these products rising from $715.5m in 2016 to $1.1bn by 2021. Growth in the Japanese market is largely driven by two factors: demand for advanced medical technologies and the increase in the elderly population.

FIGURE 2

Global Diagnostic And Guided Interventional Cardiology Product Sales By Country/Region, Combined Market Forecast ($m), 2016-2021



Source: "Diagnostic and Guided Interventional Cardiology Products Market," Meddevicetracker

One of the major drivers of growth in emerging markets is the high demand for better health-care services among the growing middle class in these markets. As health care has continued to improve in emerging markets, life expectancy has gone up, which has increased the elderly demographic and the prevalence of CVD risk factors associated with advanced age and "Westernized" lifestyles. In addition, the demand for better health care in the emerging markets has also incentivized governments to invest in improving health-care services.

While multi-national suppliers of minimally invasive diagnostic imaging devices continue to see strong revenue growth in emerging markets compared to the developed world, they are also facing hurdles in terms of doing business.

Among the biggest threats is the emergence of local rivals that can profitably operate in these countries while undercutting the multi-national suppliers. This, in particular, will impact suppliers of cardiac X-ray systems and imaging catheters, which are sophisticated and costly devices that are integral to catheterization laboratory procedures.

While Japan has always been a good target market for multi-nationals to adopt their advanced diagnostic imaging technologies, local medtech companies in China and India have succeeded in competing in these markets by offering less-costly alternatives. This, in turn, will force the multinationals to rethink their marketing strategies in these parts of the world.

Also, as health-care systems in emerging markets continue to improve and offer better services to meet patient demands, guidelines to determine which patients are suitable candidates for minimally invasive diagnostic imaging will be implemented, which will curb the use of these devices.

Meanwhile, in the US, which accounted for 35% of all diagnostic and guided interventional cardiology product sales in 2016, the rising number of people with CVD, their failure to manage risk factors until severe symptoms manifest themselves, and patients not responding to pharmaceutical therapies or refusing to make better lifestyle choices, are all paving the way to interventional therapy.

In the US, total product sales of diagnostic and interventional cardiology products are expected to rise from $1.2bn in 2016 to $1.5bn by 2021, a CAGR of 4.6%.

When it comes to the entire diagnostic and guided interventional cardiology products market, *Meddevicetracker* expects that the US will continue to domi-

nate the market in terms of product sales.

The five major EU markets -- France, Germany, Italy, Spain and the UK – accounted for 23% of total product sales in 2016, which made it the second-largest market for these types of products. Here, sales of diagnostic and interventional cardiology products are expected to rise from $805.9m in 2016 to $991.1m by 2021, a CAGR of 4.2%. The EU market is facing similar growth drivers and challenges as seen in the US.

While interventional cardiologists in developed countries have access to sophisticated, noninvasive diagnostics that may not be available in less-developed health-care systems to preoperatively diagnose patients, diagnosing disease early on remains problematic, even in the developed world.

According to Datamonitor Healthcare epidemiology forecasts, the incidence of myocardial infarction and stroke is steadily increasing in the US and EU markets, ensuring the continued need for minimally invasive diagnostic devices to guide surgical procedures treating these cases. (See Figure 3.)

Severe cases of CVD that suddenly result in stroke or myocardial infarction—of which there are hundreds of thousands of cases annually in the US and Europe alone— require surgical intervention to revascularize and restore blood flow to the brain and/or heart.

Meanwhile, doctors' preference for minimally invasive diagnostics and therapies for managing CVD cases requiring surgery has helped support the growth in product sales.

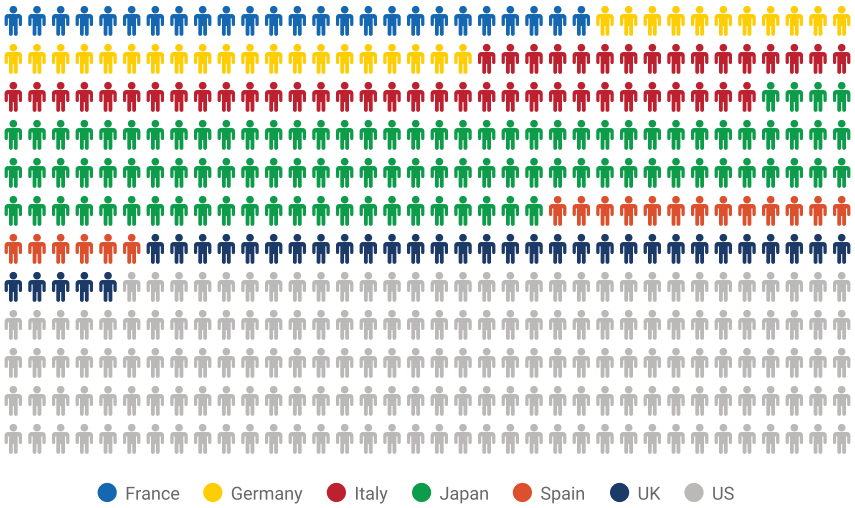
INTRACARDIAC ECHOCARDIOGRAPHY

While many of the diagnostic and guided interventional cardiology product segments can be used to perform the same types of procedures, creating competition between these technologies, ICE devices remain the exception.

ICE differs from other minimally invasive diagnostic imaging techniques used in the cath lab due to the location where the device is employed inside the body. As opposed to imaging the vasculature, ICE captures real-time information of cardiac structures that can be used in various procedures.

FIGURE 3

Incidence Rates For 2016: Estimated Incident Cases Are For Ischemic And Hemorrhagic Stroke



Source: Datamonitor Healthcare – Epidemiology, Stroke, 2017

Meddevicetracker expects sales of ICE products to rise more than the other segments, at a CAGR of 13.7% as these devices offer multiple advantages and unique features compared to other systems.

For one, ICE has shown clinical success in comparison to transesophageal echocardiography. Also, the procedural flexibility of ICE – from evaluating and deepening the understanding of cardiac mechanisms to guiding the placement of implantable pacing leads and real-time monitoring of targeted areas for cardiac ablation – is a major incentive for companies to do research and development in this area.

By providing real-time visualization of intracardiac anatomies, ICE enables shorter procedure times. Another benefit of ICE is that it potentially allows for more efficient use of cardiac laboratory resources and reduces radiation exposure for patients undergoing ablation and myocardial repair procedures, *Meddevicetracker* reported.

But ICE has some limitations.

Jeffrey Cavendish, director of interventional cardiology at Kaiser Permanente in San Diego, California, told *Medtech Insight* that while ICE is a commonly used procedure by electrophysiology doctors at Kaiser and has growth potential, he'd like to see technological improvements.

"We're doing more and more of these less-invasive procedures where we put in heart valves, plug in holes of the heart, there is a need for better technology with ICE like 3-D imaging," Cavendish noted. In that regard, he said, transesophageal echocardiograms are still a bit ahead, since they offer 3-D.

Another big disadvantage of the modality is the cost of the catheters, which are expensive single-use items currently supplied by only a few manufacturers worldwide.

ICE catheters are differentiated on the basis of cost as well as steerability and ultrasound frequencies, modes and penetration depth. In addition, ICE catheters are available with mechanical or phased array transducers. Radial ICE systems, such as **Boston Scientific Corp.'s***Ultra ICE* catheter, use mechanical transducer catheters, which are the least expensive of the ICE catheters currently on the market. Radial ICE systems offer 2D imaging with excellent near-field spatial resolution, but limited depth of penetration and no steering capability.

That said, the lack of competition from alternative diagnostic imaging techniques continues to drive the growth of ICE; and at the same time restrains sales growth that impacts other diagnostic interventional cardiology product segments.

In 2016, the competitive landscape for ICE products was dominated by four big players – Boston Scientific with its *Ultra ICE PLUS* catheter, **St. Jude Medical Inc. /Abbott International** 's *ViewFlex Ultra catheter* and **Biosense Webster Inc. /Johnson & Johnson's***AcuNav* licensed from **Siemens Healthineers'***V ICE* catheter.

Biosense Webster continues to dominate the market for ICE products with its robust portfolio of interventional electrophysiology solutions. Based on *Meddevicetracker* estimates, sales of ICE systems attributable to Biosense Webster accounted for about 63% of total ICE sales in 2016.

St. Jude Medical/Abbott was the second largest supplier to the global ICE systems market in 2016 with an estimated market share of 16%. Boston Scientific and Siemens Healthineers/Siemens product sales accounted for the remaining 21% of ICE system sales in 2016.

"That field (ICE) is definitely growing… how fast it will grow in the next few years is hard to know, but we'll be using more ICE as procedures get less invasive and are more common," Cavendish said.

FFR

Guide-wired physiologic stenosis assessment, or fractional flow reserve (FFR), is an invasive diagnostic technique used to help physicians decide whether patients with intravascular blockages would be better served undergoing percutaneous intervention or receiving medical therapy. *(Also see "ACC 2017: Trial Shows FFR-Guidance Can Help Heart Attack Patients Avoid More Revascularizations" - Medtech Insight, 24 Mar, 2017.)*

Assessing the severity of vessel stenosis based solely on angiography has shown insufficient for determining whether a patient requires interventional treatment, often leading to unneeded treatment. Unlike conventional angiography, FFR can assess the severity of the physiological impact of narrowed blood vessels and plaque buildup.

"FFR is becoming the gold-standard to assess if a blocked artery is really significant and whether or not we should put a stent in it," Cavendish said. "We have to do the angiogram first and then we put the wire down the heart artery and we measure the pressure across the blockage to see, if the pressure difference is significant."

Peter Pelikan, director of the cardiac catherization laboratory at Saint John's Health Center in Santa Monica, California, told *Medtech Insight* that the outcome data from FFR is essential in determining whether or not a lesion requires stenting. He estimated that he uses FFR in about 10-15% of his cases when the functional impact of a suspected lesion is uncertain. However, he added, that he's not using FFR unless he is able to locate the area of ischemia using a thallium stress test or nuclear stress test.

Companies that currently offer products for the functional assessment of intravascular stenosis include **Acist Medical Systems /Bracco SPA** , Boston Scientific, **Opsens Inc.** , **Philips Healthcare** and St. Jude Medical/Abbott.

Though, the FFR segment is expected to grow 10.1% by 2021, it too is facing competition from less-invasive procedures.

In particular, Cavendish foresees that another technology, instantaneous wave-free ratio (iFR), a software developed by **PhilipsVolcano**, could put a significant dent into the FFR market. *(Also see "ACC 2017: Double-Whammy Trial Data Boost For Philips' iFR" - , 24 Mar, 2017.)* Volcano's *iFR* allows physicians to obtain the same results without the use of adenosine. *(Also see " Philips splashes $1bn on Volcano" - Medtech Insight, 17 Dec, 2014.)*

"You put the put the wire down and you measure – it's pretty easy and straightforward and less expensive (compared to FFR) and faster to do," Cavendish said. "The technology in their wire is pretty good. With FFR we need to inject adenosine to dilate the heart artery."

A recent review published in the *Journal of the American College of Cardiology*, "The Evolving Future of Instantaneous Wave-Free Ratio and Fractional Flow Reserve,' stated that "currently, FFR remains the legacy coronary physiology index in common daily practice. However, the contemporary, largescale body of evidence that supports the use of iFR as an alternative to FFR challenges this legacy, particularly as iFR is quicker and spares the patient the unpleasant side effects of adenosine."

Cavendish said while most companies have developed quality guide wires (FFR), he believes that many will be looking to adopt iFR technology.

"Volcano is ahead of the game with iFR and the other companies are trying to catch up a little bit. We're probably going to do more iFR using similar systems," he added.

OCT

The fastest-growing segment in the diagnostic and guided interventional cardiology products market, optical coherence tomography (OCT), is used as a visual analog to IVUS to image the interior of the diseased arteries and acquire information on lesion length, plaque morphology, stent-vessel wall apposition and vessel diameter.

But compared to IVUS, OCT has a 10-fold higher resolution, according to *Meddevicetracker*. Coronary OCT procedures start with an injection of contrast agent through a guiding catheter to flush the blood from the artery, followed by the pullback of the OCT-wire using a pullback device. The imaging procedure is extremely fast and takes about three seconds to image an entire coronary artery. The diagnostic value of OCT in coronary applications can be further enhanced when used in combination with functional angiometry, which has proven to be highly effective in the optimization of patient selection for PCI and predicting/evaluating plausible outcomes of coronary revascularization therapy.

Still, OCT has several disadvantages including poor tissue penetration, limited use in vessels with heavy plaque burden and image obstruction by blood. The required injection of a contrast flush can also present safety issues for some patients.

Cavendish said it's for some of these reasons above that he prefers using IVUS and doesn't use OCT at all in his cath lab. He said IVUS has been around longer.

"With OCT, every time you take a picture, you have to inject the iodine contrast in the heart artery to remove all the blood, so you get a cleaner picture," he said. "And there are certain parts of the heart artery you can't really see as well with OCT. We get all the information we need with the IVUS,

but some would argue that OCT gives you better images and more definition."

OCT is dominated by two key players St. Jude Medical, now part of Abbott, and **Terumo Interventional** Systems. *(Also see "TCT 2016: OCT Improves Stent-Expansion In ILUMIEN III Trial" - Medtech Insight, 1 Nov, 2016.)* Abbott offers its *Dragonfly Optis OCT* imaging catheter compatible with the company's Optis and *Ilumien Optis* systems. Terumo offers the *Fastview* coronary imaging catheter and *Lunawave* coronary imaging console.

EMERGING TECHNOLOGIES

Innovation in the diagnostic interventional cardiology market has slowed in recent years as a result of physicians in developed markets favoring noninvasive diagnostic imaging techniques, such as stress-testing, computed tomography angiography and nuclear imaging, to preoperatively evaluate the severity of a patient's disease and determine the necessity of interventional therapies.

Doctors typically use minimally invasive diagnostic techniques in cases where noninvasive diagnostic imaging results are inconclusive. Much of the innovation that occurs takes place in software improvements for workstations and revisions to current imaging catheters and accessories as seen with iFR and FFR.

While competition between modalities has a restraining effect across device segments, some suppliers of diagnostic interventional cardiology products have been able to successfully market multi-modality systems, which give physicians greater flexibility and access to more than one modality in the catheterization laboratory.

While these devices represent a respectable percentage of supplier revenues, there is a high degree of uncertainty regarding the return on investment in new, minimally invasive diagnostic technologies due to a lack of active clinical trials.

Looking forward, *Meddevicetracker* anticipates that any significant innovation in diagnostic interventional cardiology devices will be attributable to small startups, due to the nature of these companies being less risk-averse in developing potentially innovative new technology.

One of these companies that Cavendish believes could be on the verge of something really big is **HeartFlow Inc.**, which developed the HeartFlow *FFRCT Analysis*, a noninvasive technology that provides a digital 3-D model of a patient's coronary arteries in conjunction with its FFR and iFR and IVUS catheters.

HeartFlow inked a collaborative agreement with **Royal Phillips** on Aug. 28 to promote HeartFlow's technology in conjunction with its own FFR, iFR and intravascular ultrasound advanced catheters. *(Also see "Philips, HeartFlow Cut FFR R&D, Commercial Deal" - Medtech Insight, 30 Aug, 2017.)* The collaboration will initially focus on the US with the intention to expand globally in the near term.

"That company is potentially on the breakthrough of something really big," Cavendish said. "We're looking at the CT angiography and then based on those pictures, if there is a blockage of the heart arteries, then the HeartFlow technology can estimate if the blockage is severe enough to warrant a stent. That's pretty exciting."

He said that most hospitals are starting to look at HeartFlow and Kaiser will start using the technology in October. Siemens Healthineers entered into a collaborative agreement with HeartFlow last March and **GE Healthcare** also struck an agreement this July, giving the technology other votes of confidence.

Another technology that is making its way into operating rooms and cath labs are robotic-assisted surgical systems. A potentially lucrative area of growth— so long as certain limitations can be overcome by manufacturers of these systems – combining telecommunication and robotic systems is one type of innovation in robotics that holds much promise.

A study (REMOTE-PCI study) led by Ryan Madder at Spectrum Health, Grand Rapids, Michigan where interventional cardiologists performed PCI on 20 patients remotely achieved technical and procedural success rates of 86.4% and 95.0% respectively, according to TCTMD news.

The concept of telestenting has potential applications and would offer physicians certain advantages, Cavendish agreed.

"The big upside is that as the operator I can sit down and I'm away from the X-ray exposure," Cavendish said. "I can take my lead off. With all the occupational hazards with what I do; wearing the lead, being on my feet all day and the radiation exposure, this technology dramatically decreases that."

Another team of researchers at the University of Bristol is developing a three-piece robotic-assisted surgical system that consists of an exoskeleton glove that would allow surgeons to control minimally invasive devices from inside patients.

The minimally invasive device placed within a patient will feature haptic feedback, which will enable surgeons to "feel" tissues, as well as a gripper designed to mimic the thumb and two fingers of a human hand for more natural orienting and operation. The third component of the system will be smart glasses which provides the surgeon with a real-time view of the procedure from outside of the operating room – reducing the surgeon's exposure to radiation and limiting orthopedic strain on the surgeon.

Meanwhile, in 2016, industry giant Medtronic announced it intends to launch its own surgical robotic system. The unnamed surgical robotic system will be able to perform all procedures that current robotic-assisted surgical systems can perform, Medtronic said.

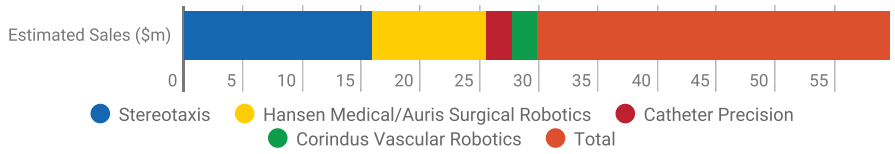
The company said it plans to introduce the robotic system to markets outside of the US first in fiscal year 2018 and in the US in 2019. It is anticipated that Medtronic's future market entry into the robotic-assisted surgical systems market will disrupt the business of current competitors.

Currently there are four suppliers of robotic-assisted surgical systems indicated for use in interventional cardiology cases.

Stereotaxis Inc. accounted for the largest market share, 53%, in 2016 with its *Niobe Magnetic Navigation System*and the *Vdrive Robotic Navigation System*. **Hansen Medical Inc.**, which was acquired by **Auris Surgical Robotics Inc.** last July, was the second-largest supplier of robotic-assisted surgical systems in 2016, with an estimated market share of 32.6%. Hansen Medical offers the *Magellan* and *Sensei* robotic systems. **Catheter Precision** and **Corindus Vascular Robotics Inc.** accounted for

FIGURE 4

Global Robotic-Assisted Surgical Systems Market, Share By Supplier, 2016



Source: "Diagnostic and Guided Interventional Cardiology Product Market," Meddevicetracker

7.4% and 7% of total estimated product sales in 2016, respectively (Fig 4).

One of the major barriers to wider adoption of robotic systems is cost. Based on *Meddevicetracker* estimates, the average sale price of robotic-assisted surgical systems ranges from $250,000 to as high as $1.5m. *(Also see "US FDA Advisory Panel Backs Claret's Sentinel TAVR Filter" - Medtech Insight, 24 Feb, 2017.)*

One way that companies developing robotic-assisted surgical systems have tried to overcome the cost barrier is leasing the capital equipment and then selling the consumable products required to operate these systems at a premium price. Robotic-assisted surgical system suppliers generate a significant portion of their annual revenues through the sale of consumable products.

Despite the disadvantages associated with robotic-assisted surgical systems – such as limited surgical complexity, device cost, reimbursement, and the cost-conscious environment of health care in many countries – there are a number of other advantages that robots provide.

Besides reduction in radiation exposure for the operator, robotic systems lower the risk of orthopedic injury for the operator, have shown to reduce major complications, improve visualization and guidance and offer patients faster recovery times.

But Cavendish said it's hard to know where robotic-assisted technology will go in interventional cardiology and whether it will take off.

"It's a little bit of an ego thing, but I don't think the robot is better than me in what I do," he said.

Still, compared to other diagnostic and guided interventional cardiology product segments, technological innovation is on the rise in this segment.

Published

WATCH

To watch a video of Philips Volcano's IVUS FFR tech in action and how it will work with HeartFlow's FFRCT, go to http://bit.ly/2z3EiVL

Change At Helm As Tissue Regenix Enters Next Growth Phase

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Anthony Odell, who has been leading **Tissue Regenix Group PLC** for nearly a decade, is stepping down as CEO. His departure, announced Oct. 18, comes two months after he oversaw the closing of the regenerative medicine firm's acquisition of **CellRight Technologies LLC** (CRT), a young Texas start-up specializing in bone regeneration. *(Also see "'Profitable, High-Growth' CellRight Bulks Up Tissue Regenix's Ortho Biz" - Medtech Insight, 20 Jul, 2017.)*.

Leeds, UK-based Tissue Regeneix told *Medtech Insight* that Odell had left with the agreement of the board of directors "as the business is moving into a new phase of development." It maintained that board still stood by the acquisition of CRT and "the sound strategic sense" of the deal. "[The] integration continues and we will report this progress in due course. As reported at the interim results, we are comfortable with the progress of the group, including CRT, and there have been no material changes to report."

The firm will start its search for a new CEO and in the meantime, John Samuel, non-executive chairman, will take on the role as executive chairman.

Jefferies analyst Chris Cooper noted that the change in leadership was likely down to the board wanting a CEO with more commercial experience and integration expertise. While Odell's achievements at Tissue Regenix have been significant, including overseeing the firm's IPO and several key product launches as well as its first M&A deal, the company has also missed several commercial and development targets, Cooper pointed out.

"[With] several products at a crucial stage of commercialization and the integration of a larger, more established business ongoing, the Board likely felt the role now requires a different skill set. Longer-term we believe the previous CEO of CellRight could be a suitable candidate but the Board may prefer to look closer to home for now," he speculated.

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Teamsters Ask Stockholders To Replace Cardinal Health Chairman

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Shutterstock: SherryYatesYoung

The International Brotherhood of Teamsters is calling on Cardinal Health stockholders to relieve Chairman and CEO George Barrett of his chairman duties, and appoint an independent board chairman, saying Barrett has failed to "set the correct tone at the top," as the company has become more entangled in the US opioid epidemic.

In a proposal that will be presented to Cardinal Health shareholders at their stockholders meeting Nov. 8, the Teamsters labor union, which holds hundreds of shares of Cardinal stocks on behalf of its members' pension fund, said the current leadership "has proven inadequate in tackling Cardinal Health's role in fueling the opioid crisis." The union cited several charges and recent settlements by the US Drug Enforcement Administration (DEA) against Cardinal for drug-distribution violations.

Among the settlements was one in January, in which Cardinal agreed to pay $20m to settle allegations by the state of West Virginia that the company acted "negligently" and "recklessly" by distributing more than 241 million prescription opioid pills over a six-year period to a state with only 1.8 million people.

A similar campaign by the Teamsters targeting **McKesson Corp.**, another drug distributor with a medical supplies and device business, was successful this summer in driving that company's board to agree to split the CEO and chairman role once John Hammergren, who currently holds both positions, steps down.

Cardinal had sales of $130bn in 2017, and was ranked fifth, internationally, in overall medtech revenues in *Medtech Insight*'s most recent MTI 100 rankings. Among Cardinal's specialties and businesses are the manufacture and distribution of wound care and infection control products, surgical supplies, and durable medical equipment, in additional to its pharmaceuticals distribution business.

CHARGE: EXCESSIVE BONUS PAYMENTS FOR LARGE OPIOID ORDERS

Cardinal – along with other large drug distributors – also failed to alert the agency to suspiciously large orders of prescription opioids in Alabama, New York, Ohio, Oregon and Kentucky, the Teamsters charged in their proposal 5 to Cardinal shareholders. The company continues to be investigated by several state attorneys general on drug-distribution charges, and for providing incentive bonuses to employees for negotiating large contracts for sales of opioids. *(Also see "Opioid Industry's 'Superstructure' Targeted By State Attorneys General" - Medtech Insight, 19 Sep, 2017.)*

The union also said that Barrett's involvement in the company's pay practices needs to be overhauled, specifically for its excessive bonus payments to its regulatory and compliance officers, including to Chief Compliance Officer Craig Morford. For example, the Teamsters wrote, every year from 2010 to 2016, Barrett, in conjunction with the board's Compensation committee, "saw fit to award Mr. Morford an annual incentive bonus that was significantly above target, even as the agency was paying out tens of millions of dollars to settle DEA claims, and even though Mr. Morford's bonus is supposed to reflect the effectiveness of Cardinal's regulatory and compliance program."

Barrett himself was compensated a total of $13.66m in fiscal 2016, through the combination of a $1.32m salary, $9.82m in stocks and stock options, and approximately $2.52 million in incentive bonuses and other compensation, according to a Cardinal Health 2017 Proxy Statement filed with the Securities and Exchange Commission. But the Teamsters said that Barrett "was also the recipient of considerable largesse," and was compensated more than $127m over 2014, 2015, and 2016. Barrett declined to accept an annual incentive payout this year, so his total compensation was $10.98m for 2017.

In comparison, **Johnson & Johnson** CEO Alex Gorsky, was paid $21.2m total in 2016, outgoing **General Electric Co.** (includes the **GE Healthcare** subdivision) CEO Jeffrey Immelt had an $18m package upon leaving the firm in mid-June, and **Siemens AG** CEO Joe Kaeser's compensation was about $7.62m in 2016.

CARDINAL HEALTH BOARD DEFENDS BARRETT'S ACTIONS

But Cardinal's Board of Directors believe that Barrett's pay is appropriate, and recommended a "no" vote on the Teamsters' proposal, saying that Barrett "has been effective as shown by our strong performance over the past several years." The directors added that the board and management "have been actively engaged on the opioid issue," and has maintained a "robust system of controls to detect and report suspicious orders" of pharmaceuticals.

"The board believes that Mr. Barrett is best suited to serve as chairman because of his unique knowledge of our business, the health-care industry, and our shareholders," stated the directors, and recommended a vote against removal of Barrett as chairman.

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Novacyt Raises €9.7M, Ahead Of UK IPO

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Diagnostics firm **Novacyt SA** has raised €9.7M ($11.5M) ahead of a dual listing on the London Stock Exchange Alternative Investment Market (AIM).

Novacyt, which is currently listed on Euronext Growth Paris exchange, raised €4.7 million through a conditional placement of almost 7.1 million shares, and €5.0 million through an unconditional direct subscription of nearly 7.7 million shares. Both had an issue price of 59.38 pence per share. The funds were raised through a combination of Novacyt's investor base in France and new UK institutional shareholders.

Graham Mullis, CEO of Novacyt, told *Medtech Insight* that the proceeds would be used to accelerate the company's ambitious growth plans with R&D investments. "We've been expanding manufacturing capacity and we have a new facility that just opened in Camberley, Surrey. We want to invest in other parts of manufacturing operations and continue to expand our commercial infrastructure, adding more people to the sales team," Mullis said. Product development will be another key focus for the company as it plans to obtain CE-IVD approval for the *Primerdesign* research products gained through the acquisition of Primerdesign in 2015.

Cambridge, UK-based Novacyt is the first health-care company to be dual listed on both the London AIM market and Euronext Growth Paris. "It's nice to pioneer," Mullis said. "This UK IPO was a long process that involved multiple advisors to help us achieve a momentous transaction so we are all very proud."

Novacyt said London AIM was the most suitable market for the company's growth plans due to the company having an increasingly UK focus. "Following the acquisition of Primerdesign last year, we have about 90% of our operations based here in the UK so we've become very much a UK centric business. In addition, we have reached quite a key point in our lifecycle as a business and we want to realize our ambitious growth plans and having an AIM listing will enable us to realize those plans."

"The AIM market is potentially larger than the Euronext Growth market in Paris and there are a much larger and higher number of institutional shareholders for which Novacyt could be attracted to," Mullis said. "The next focus will be to continue to drive the business hard and deliver results. For the first time in the company's history we are adequately capitalized going forward to drive that growth and we are delighted that we have a well-capitalized balance sheet."

The shares from the €4.7 million conditional placement are expected to be issued on Nov. 1, with AIM admission taking effect on that date. The €5.0 million first tranche of subscription shares has been unconditionally issued, and admission of the shares are expected to take effect on Oct. 19 on the Euronext Growth Paris exchange.

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Medovex Plans US IDE Trial For Its DenerveX Spine Surgery Device

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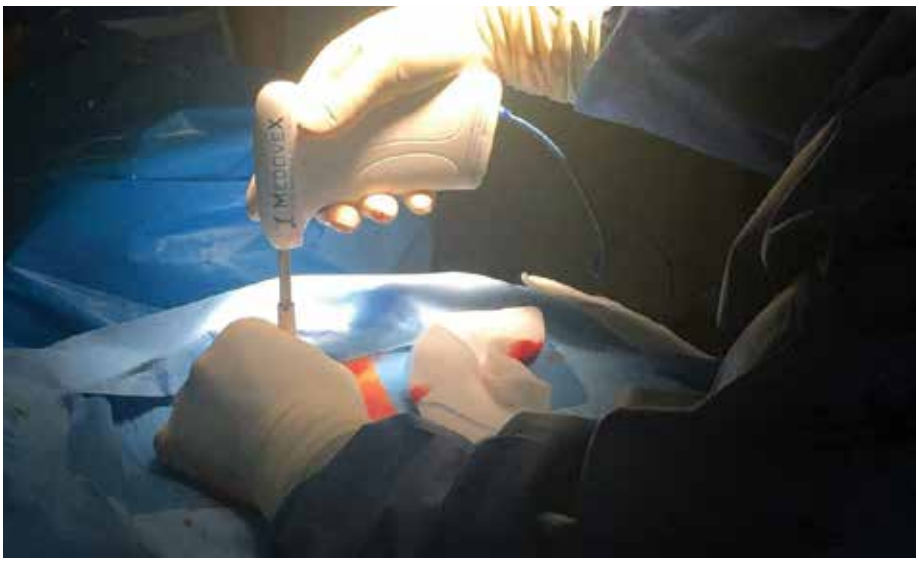
Medovex Corp. hopes the recent European launch of its *DenerveX* spine-surgery device to treat back-pain caused by facet joint syndrome, along with the start of a US pivotal trial, will reinvigorate investor interest in the company, which went public in 2014.

Scott Haufe, a Destin, Florida anesthesiologist, first developed the DenerveX concept after noticing that the pain-relief benefits of rhizotomy – a surgical procedure to ablate the nerve roots in the spinal cord with radiofrequency energy – were often temporary, because the nerve root would regrow and attach to the capsule.

Haufe developed a procedure to ablate the nerve as in a traditional rhizotomy, but



also remove the capsular tissue within the joint that contains the peripheral nerve endplate receptors, to prevent the nerve from regenerating. It works because the dorsal root axons are incapable of re-innervating the joint without the endplate receptors in the joint. In a 174-patient trial of this approach, 77%, 73%, and 68% of the patients with cervical, thoracic, or lumbar disease, respectively, showed at least 50% reduction in pain at least three years after the procedure.

The new endoscopic facet procedure offered better long-term relief than facet steroid injections or rhizotomy procedures when comparing outcomes in the subset of trial patients who had previously tried one of those procedures. Also, no infections or nerve damage beyond the intended nerve ablation was observed.

However, the two-step procedure took an average of 17 minutes per joint, and most patients required treatment of at least four joints, so Haufe began developing what would become the DenerveX device – an RF-ablation delivery device with a rotating shaft that could be used perform both parts of the procedure rapidly.

DenerveX is sold as a disposable, single-use kit compatible only with the *DenerveX Pro-40* generator, which stays in the physician's office.

"One of the benefits we're looking at is that we have a non-opiate or non-pharmacological derived pain-relief system," Medovex executive co-chairman Jesse Crowne told *Medtech Insight*. He pointed out that lower back pain is the most common symptom of patients prescribed opiates. "We have a device that comes in earlier in the continuum of care and gets them out before they are ever prescribed an opiate. That could have a meaningful impact in the opiate epidemic. That's an added benefit to this particular procedure because we're getting the long-term pain relief for patients who are in debilitating pain and don't have very many other options."

'AN ATYPICAL PATHWAY'

Medovex was first incorporated in Nevada on July 30, 2013, as Spinez Corp, the parent company of Debride Inc., co-founded by Haufe and serial biotech entrepreneur Steve Gorlin. The company changed its name to Medovex in 2014 and the firm went public on the NASDAQ at a share price of $5.75 at the end of 2014 and closed an over-allotment option one month later, for total proceeds of $9.2m. *(Also see "Deals Shaping The Medical Industry, February 2015" - Medtech Insight, 6 Feb, 2015.)* However, the shares have been languishing below $2 for about two years and are now listed around $1.15.

Photo credit: Medovex Corp.

Medovex Executive Co-Chairman Jesse Crown

Crowne took over Gorlin's role as director and executive co-chairman of the company in August after serving as acting VP-Business Development since January 2015. He is also a managing partner of Gorlin Companies (run bySteve Gorlin) the single-family office specializing in founding and funding early ventures. Medovex's other co-chairman is Larry Papasan, a former president of Smith & Nephew Orthopedics, and the CEO is Steve Gorlin's son Jarrett Gorlin, the former president of Judicial Correction Services, a private probation company in Atlanta.

"This is an atypical pathway for a company, especially in the medical device arena," Crowne said. "It's more common in biotech and most of Steve Gorlin's success has been in biotech, so we've tended to follow that model. It has not been proven to be as fruitful as it would be in a biotech company. We've been punished by the public markets for coming out too early."

DenerveX earned a CE mark in June and the first in-human procedure was completed in July inManchester, England. The company is training physicians and selling the system commercially in Switzerland, Spain, Italy, the UK and Germany *(Also see "OUS Approvals: Neurostim And Cardiovascular Lead June Surge" - Medtech Insight, 20 Jul, 2017.)* DenerveX earned approval in Australia in August.

DenerveX is a "a highly complicated device that has been pieced together in a very intuitive method," and so far the response from the spine-surgery community in Europe has been very positive, Crowne said.

"We intended to just stay in UK and Germany through the third-quarter of this year, but the training did well and we spent a long time working with physicians and making sure there were no adverse events," Crowne said. "Once the physicians picked it up very quickly, we realized we could accelerate the training and roll-out to Italy, Spain, and Switzerland, and then got approval in Australia about six months ahead of schedule." He said the company already has orders for it in South American and hopes to begin providing it to surgeons there in the fourth quarter.

"Now that we're at the point where we are commercializing, we can start to build some shareholder value. Because this is a Gorlin company, we have several high-net-worth individuals who have tended to back our deals and we will continue to work with those investors to make sure we have adequate capital for the company," he said.

Medovex will target the US market by filing an investigational by the end of this year for a 150-patient non-inferiority trial. The trial will compare the DenerveX procedure to rhizotomy alone. The trial will be designed to show non-inferiority of the DenerveX procedure to rhizotomy at six-months, with the potential to show superiority after two-years of follow-up. This will give the company a chance to get the device in the US market as soon as possible while preserving the chance to show potential customers that it is superior to the rhizotomy later.

Medovex has previously told shareholders that it hopes FDA will clear DenerveX via the 510(k) route, but that the company is budgeting for the possibility that it may require a more data-intensive PMA.

The company is also running a European registry for DenerveX and may ask

FDA to allow it to roll the data into its IDE study. The downside of that approach would be that the company could not announce any of the registry results until the IDE trial is over, which could limit its near-term marketing message options.

"We haven't made any announcements on the need to raise capital, but the trial will likely cost more than what we have today," Crowne said. As of June 30, the company had about $749,000 in cash on hand after recording a loss of $3.47m in the first six months of 2017. That is an improvement from the $9.4m loss reported for the first six months of 2016.

Crowne said that for the foreseeable future, the company will be focused on entering the US market and continuing to commercialize DenerveX, but eventually hopes to adapt the technology to other pain treatments. "We're going to build this to be a very big product and we do see iterations in other pain sources. [But for now,] we want to stay focused on really validating the technology in the spine space in particular," he said.

The company may also be an acquisition target for larger diversified orthopedic surgery device companies in the future. "I do think there will be some acquisitive interest from some of the larger players and we would absolutely entertain conversations with them," he said.

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START-UP SPOTLIGHT:

LUMICELL: Shining The Light On Real-Time Intraoperative Tumor Detection

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Of the 300,000 cancer lumpectomies that take place in the US each year, over 60,000 of these patients undergo a second surgery to remove tumor tissue that had been missed in the first procedure. These re-excisions not only cause additional discomfort and a negative emotional and cosmetic impact on the patient, they can also cost the health care system up to $1bn each year.

"This is a huge challenge that is faced by the patients, the physicians and the payers. Currently, there are no marketed product that ensures surgeons get clean margins during the cancer surgery. As a result, the surgical procedure takes a long time, [documented evidence has shown that] the surgeons take out 30-50% more tissue than necessary, and another 20-30% of the time the surgeons leave cancer behind. This is a significant issue in cancer management," says Kelly Londy, CEO of **Lumicell, Inc.**, a Massachusetts firm seeking to address this problem.

The company's *LUM* system is designed to enable surgeons to see, in real-time during the operation, residual cancer in the tumor bed so that they can remove all the cancer cells in that one procedure.

The technology has three components: a proprietary fluorescent optical contrast agent, *LUM015*; a hand-held imaging device; and proprietary decision software. The LUM015 optical contrast agent is administered to the patient before surgery as part of the normal pre-op preparation. The agent naturally permeates the tumor micro environment, towards "the invasive front," where cancer cells interact with associated immune cells such as macrophages, two cell types that secrete more of the cathepsin protease than healthy cells. As the LUM015 is protease-activated and enzymatically cleaved, it gives off a fluorescent glow when interacting with these cells.

During the surgical procedure, after the surgeon removes the bulk of the tumor, they use the LUM imaging device to scan the cavity wall and see where the LUM015-activated fluorescent cancer cells are. The LUM decision software tool is used to display that image from the cavity directly onto a monitor, and the surgeon can proceed to remove any remaining cancer cells then and there. The LUM system is designed to be integrated easily into the current workflow for cancer surgery, without surgeons having to make any significant changes to the standard procedure, Londy told *Medtech Insight*.

Early data of the technology's performance have been promising. Results from the first phase of a feasibility study at Massachusetts General Hospital (MGH) showed that the LUM system could differentiate between tumor and normal tissue in vivo and ex vivo with administration of LUM015 just a few hours before the surgery. Most importantly, the system demonstrated the ability to detect 100% of residual cancer.

Based on these results, Lumicell is moving onto the second phase, a pivotal trial with an expanded cohort of breast cancer patients, where the LUM system will be used in vivo to guide the re-section of tumor and evaluate the reduction in positive margins and re-excisions.

If everything runs smoothly, the company believes the system will be approved and ready for commercial launch in the US in late Q1 of 2019.

While breast cancer is the first target indication for the LUM system, the company is investigating applications for the technology across multiple cancers and is currently in human trials for prostate, colon, pancreatic, and esophageal. Lumicell is also preparing the clinical trial protocols for ovarian and brain cancers.

In terms of competition, there are other companies and drugs that have been

around for 15 years of so, using spectroscopy and some luminescence that are looking at the actual tumor, Londy said. "We are not aware of anything that is so far ahead in development as we are, [a system that incorporates] a drug, a device to look at it with and a decision software – there's nothing available on the market now. I think we will be the first on the market with the complete solution," she said.

The company has been busy fundraising this year; it brought in $13.5m from first tranche of a series C in the summer this year and earlier in October, it raised $14.2m in a second tranche, bringing the total series C round to $27.7m. These funds will enable the company to take the LUM system all the way through its breast cancer clinical trial and to the point of commercialization. In addition to equity funding, the firm has also had $18.8m in non-dilutive funding through grants and collaborations with the medical centers, which has financed the clinical trials so far.

Lumicell's key customers for the LUM system would be surgeons, but the hospital administrator who controls the purse strings would also be a target influencer, Lumicell has identified, in the purchase decision-making process. As the LUM system "speeds up efficiencies to the OR and improves hospital costs by reducing the need for second surgeries," this should help the firm get buy-in from the hospital administrator.

The company is currently working on its reimbursement strategy, although Londy said that there are existing bundled reimbursement packages in the US that could cover the LUM system. The CEO is confident, however, that adoption of the technology will not be hindered too much by its reimbursement status. "Even without having the additional reimbursement, and being bundled within what they are already doing, hospitals will see the economic benefits when they see a significant improvement in their OR time - as we are able to free up 30% of the time used for doing cancer surgery, it increases the hospital revenue."

For Londy, who took the helm at Lumicell very recently in July, her immediate priorities are to get the technology through the current breast cancer pivotal trial and approved by the US FDA. She will also be overseeing the global strategy launch, where her broad experience working at multinationals like Accuray, GE Healthcare and Philips, will prove valuable.

Driving the other indications through the FDA process, to end up having a platform launch strategy that is looking to launch one or two new indications a year.

"Driving the pivotal trial, for efficiency and appropriate FDA process, is something that is important that we are going through now and it's a priority for me, along with having a commercial activation process; making sure we are fully prepared to launch the product as soon as we have FDA approval and then implementing a global strategy," Londy said. "The benefit I bring with me is really being able to think through where to launch globally, by indication, how to launch, developing the partnerships you need with the KOLs – globally and within each different kind of indication – and maximizing the capacity for revenue as we launch."

The CEO believes a key component for Lumicell's success will be KOLs – from academic centers to community hospitals – who can demonstrate the benefits of this technology. "The product goal is to ensure every surgeon around the world has the ability to do the same high quality and quantity of surgery outcomes as the largest university in the world," Londy said. "To do that, we need to implement an easy-to-use technology and optimizing the platform so it can be used in rural community hospitals as well as in major academic centers."

While the firm is still deciding what its final commercial model will be, Londy told *Medtech Insight* that she is open to having distribution and corporation partners to help with the sales and marketing. "The more feet on the street you have, talking about the benefits of the technology and educating the customers, the better your uptake is. So, having distribution partners, commercial activation partners, is something not off the table."

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Website: www.lumicell.com

Contact: Kelly Londy, CEO

Industry segment: Cancer management

Business: Real-time, intraoperative margin assessment system using imaging techniques to guide cancer surgery.

Founded:2008

Founders: W. David Lee (Lumicell, Massachusetts Institute of Technology); Moungi Bawendi (Massachusetts Institute of Technology); Ralph Weissleder MD, Ph.D. (Massachusetts General Hospital, Harvard Medical School)

Employees: 17

Financing to Date: $34.4m equity investment; $18.8m grants

Board of Directors: Andrey Zarur Ph.D. (Green Light Biosciences); Moungi Bawendi Ph.D. (Massachusetts Institute of Technology); David Furneaux (Kodiak Venture Partners); Kevin Krenitsky, MD (OpGen Inc.); W. David Lee (Lumicell, Massachusetts Institute of Technology); Kelly Londy (Lumicell); Jim Schuermann (Medtronic); Ralph Weissleder MD, Ph.D. (Massachusetts General Hospital, Harvard Medical School)

Scientific Advisors: Bruce Chabner MD (Massachusetts General Hospital – Clinical Chair); Ralph Weissleder MD, Ph.D. (Massachusetts General Hospital, Harvard Medical School); David Kirsch MD, Ph.D. (Duke University Medical Center); Moungi Bawendi Ph.D. (Massachusetts Institute of Technology – Technology Chair); Linda Griffith Ph.D. (Massachusetts Institute of Technology)

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