Medtech Insight
Issue 71
medtech.pharmaintelligence.informa.com
Pharma Intelligence Informa
November 27, 2017

Rivals Catching Up To Intuitive Surgical In Fast-Growing, Fast-Innovating Robotic-Assisted Devices Market

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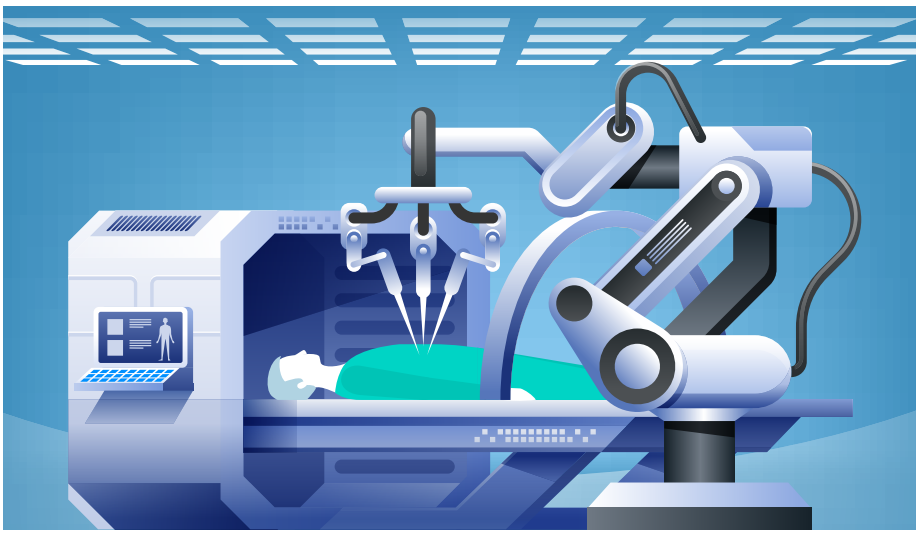
In the minimally invasive surgery space, the robotically assisted systems (RAS) market is one of the hottest and fastest-growing areas, driven by Sunnyvale, California-based **Intuitive Surgical Inc.**, which has led this market for more than a decade in soft tissue applications and continues to innovate. *(Also see "Robotic-Assisted Surgery: Taking MIS By Storm" - Medtech Insight, 26 May, 2016.)*

The billion-dollar company, however, is facing rising competition from other RAS device makers developing next-generation products that are less costly and offer advanced features -- from advanced imaging, machine learning and data analytics, eye-tracking software and navigation systems -- designed to further decrease trauma and invasiveness of surgery while offering surgeons greater precision and efficiency.

According to *Meddevicetracker's* "Robotically Assisted Surgical Devices Market" report, the global RAS market, which is divided into three segments -- instruments and accessories, RAS systems and services – is expected to rise from $3bn in 2016 to $5.3bn by 2021, a CAGR of 11.7%. (See Figure 1.)

In 2016, instruments and accessories accounted for 52% of global sales. This segment is expected to see the second-highest growth from $1.6bn in 2016 to $2.9bn by 2021, a CAGR of 13%, driven by rising procedure volumes and higher cost of advanced instruments.



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Meanwhile, sales of RAS systems in 2016 accounted for 29% of the total market share. Robot sales are hampered in large part by high acquisition costs, which range from $400,000 to $2.5m. Over the forecast period, sales of RAS systems are expected to see the slowest growth from $892m in 2016 to $1.1bn by 2021, a CAGR of 5%.

The rising installations of RAS systems, however, will translate directly to higher services revenue, generated from maintenance and repair contracts. While the services segment accounted for the smallest market share in 2016 at 19%, it is expected to see the biggest growth, rising from $581.5 in 2016 to $1.3bn by 2021, a CAGR of 16.8%.

COMPETITIVE LANDSCAPE

da Vinci

Intuitive continues to lead the global market for RAS systems with an 88.8% market share and about $2.7bn in sales of its *da Vinci* systems, instruments and accessories and services in 2016.

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

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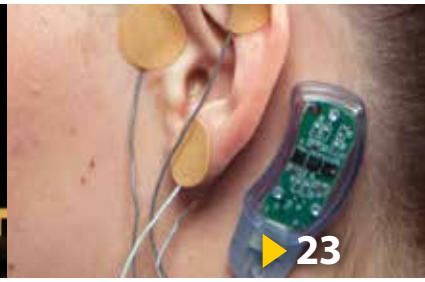

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Medtech insight

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A New York Minute: US FDA Leverages State's Health Department To Expedite NGS Reviews

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US FDA took an important step to advance policies for laboratory-developed tests services and next-generation sequencing with a Nov. 15 *de novo classification* of a tumor-profiling system.

The *de novo* in question was granted – with a class II, 510(k) risk designation – to *MSK-IMPACT*, a next-generation sequencing (NGS) system, developed as a clinical-grade test at Manhattan-based Memorial Sloan Kettering Cancer Center to help assess tumors and inform cancer treatment.

It took an unusual route to gaining FDA go-ahead through the New York State Department of Health.

The MSK-IMPACT system, which can identify the presence of mutations in 468 unique genes, had previously been approved by the NYSDOH as a clinical test, allowing the facility to offer testing with the system to patients based in the state of New York. That is the standard approach for this type of lab-developed test (LDT), developed in-house by sophisticated labs like MSK, which intend to do the testing themselves rather than sell an assay for other labs to run. New York, perhaps along with California, has the strictest procedures and checks in place before allowing LDTs to go into use.

What's new here is that MSK followed up its New York designation with a *de novo* submission to FDA "including and extending" the information that was previously submitted to NYSDOH. The New York agency's prior-review informed and expedited FDA's review, the federal agency says. More significantly, FDA is using this as a precedent to expedite future reviews of tumor-profiling systems.

NY STATE: THIRD-PARTY REVIEWER

In conjunction with the MSK-IMPACT authorization, the agency announced its recent official designation of NYSDOH as a third-party 510(k) reviewer, and it publicly announced that designation. As a result, developers of NGS-based tumor profiling tests will not need to submit anything directly to FDA in the future. Once approved by NYSDOH, the laboratory may choose to request that its state application, as well as the state's review memorandum and recommendation, be forwarded to the FDA for possible 510(k) clearance, under the newly established class II category.

To be clear, FDA is not lifting its long-held enforcement discretion policy for LDTs, which the agency says will allow laboratories designated as "high complexity" under the CLIA system to launch test services without FDA review. But the third-party designation of NYSDOH (combined with the class II, 510(k) designation) potentially allows labs to gain FDA clearance without having to submit extra data or go through new bureaucratic steps. FDA also says it might accredit other third-party reviewers for this purpose.

"As this field advances, we are modernizing the FDA's approach to the efficient authorization of laboratory tests from developers that voluntarily seek 510(k) clearance," FDA Commissioner Scott Gottlieb said. "This is another example of where the FDA is working to find creative and flexible approaches to regulation that spurs development and efficient delivery of innovative technology."

Last year, FDA was on precipice of establishing a regulatory framework that would have required some LDTs, particularly those in the highest risk categories, to seek pre-market FDA re-

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Third-Party Review Program

The third-party 510(k) review program was formally established back in 1997 with the FDA Modernization Act, but it has not attracted the level of participation initially envisioned. Manufacturers are supposed to benefit by not having to pay a user fee and by getting a quicker review for qualifying products. Companies, however, have not experienced major efficiency benefits, in part due to time taken by FDA's re-review of third-party assessments.

But In the past year, FDA has accredited two new organizations as third-party reviewers – NYSDOH and AABB, which is a standards developer for transfusion medicine and cellular therapies – bringing the total number of accredited organizations to seven. And, additional changes are in the works in conjunction with the MDUFA IV user-fee program that launched Oct. 1. FDA committed to eliminating re-reviews while strengthening the accreditation process, and it also gained expanded authority from Congress to broaden the types of devices that can employ third-party, rather than FDA, reviews.

view, but that plan was shelved after the election of Donald Trump. *(Also see "FDA Passes The Buck On LDTs, But Floats Ideas" - Medtech Insight, 13 Jan, 2017.)* Gottlieb has previously signaled his interest in streamlining FDA's role in LDT oversight and ultimately believes Congress should step in to create a new system.

"We might not have one announcement, but a series of announcements about places where we think we could create frameworks that allow for voluntary means for seeking a 510(k), if you want to, through an efficient process," Gottlieb noted in an interview with *Medtech Insight* earlier this month, likely previewing the MSK-IMPACT announcement. "But generally, I think this is an area that I'd like to work with Congress on." *(Also see "Q&A Exclusive: FDA Commissioner Talks About His Tenure, Recruiting And LDTs" - Medtech Insight, 7 Nov, 2017.)*

One approach that Gottlieb has floated as a possible framework for LDTs is so-called "pre-certification," a concept that FDA is currently investigating for digital health tools and direct-to-consumer genetic screening tests. *(Also see "'Excellence' In Health-Software Design: US FDA Taps Nine Firms To Figure Out What That Means" - Medtech Insight, 26 Sep, 2017.)* The approach puts more emphasis on the quality and dependability of the operations carried out by product-developers than on product-by-product assessment. That overlaps with how LDT-makers are currently assessed – although the NYSDOH approach and federal CLIA system includes individual test assessment, there is a heavy emphasis on certifying laboratory operations and personnel.

THREE TIERS FOR TUMOR PROFILING

The MSK-IMPACT system is the second NGS tumor-profiling system approved by FDA this year. In June, FDA approved **Thermo Fisher Scientific Inc.**'s *Oncomine Dx Target Test*, the first assay to be approved as a multi-drug companion diagnostic. *(Also see "Podcast: Thermo Fisher Talks Regulatory Experience With Oncomine" - Medtech Insight, 6 Jul, 2017.)* Oncomine had a higher, PMA standard to reach because it was expressly approved as a companion diagnostic – labeled to direct patients to one of several specific lung-cancer drugs.

In a document recently posted by FDA on its website, it laid out its "three-tiered" approach to NGS tumor-profiling systems:

- Level 1 companion diagnostics requiring the most rigorous data support, including analytical validation and a clinical study;
- Level 2 biomarkers for cancer mutations "with evidence of clinical significance," which require analytical validation and demonstration of clinical validity, typically based on publicly available clinical evidence; and
- Level 3 biomarkers for cancer mutation "with potential clinical significance," which should be supported with analytical validation and a "clinical or mechanistic rationale" for performing the test.

FDA says that once an NGS system like MSK-IMPACT gains an FDA authorization, it should be able to fluidly move genetic mutations included on the panel from level 3 to level 2 without an additional FDA submission.

"NGS technologies can examine hundreds, if not millions, of DNA variants at a time; and we are only at the beginning of realizing the true potential for these devices to assist patients and their health-care providers in learning about the genetic underpinnings of their disease," said Jeffrey Shuren, director of the FDA's Center for Devices and Radiological Health. "This collaboration is an excellent example of how the FDA can partner with the medical and development communities to review innovative tests as quickly as possible."

Published online 11/15/17

Reimagining The 'Case For Quality': FDA Looking At More Hands-Off Approach, CDRH Director Shuren Says

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US FDA is looking to form a "collaborative community" to help it step back a bit from its role as a ringleader for the Case for Quality initiative it created six years ago, the head of the agency's device center says.

Center for Devices and Radiological Health Director Jeffrey Shuren claims that by taking a more hands-off approach, FDA would help strengthen the Case for Quality. The scheme – which the agency co-leads with the Medical Device Innovation Consortium (MDIC) – aims to change industry thinking from a compliance mindset to one of sustained quality throughout manufacturing organizations.

CDRH Director Jeffrey Shuren

FDA views the Case for Quality "as a terrific opportunity for instantiating what we call a 'collaborative community,'" Shuren said Nov. 15 at an MDIC Case for Quality Forum in Washington, DC.

When there is a pressing issue in industry, "traditionally it is FDA that will go off and solve the problem. But over the past few years we have more and more pushed for [collaboration] with others," he said. Nevertheless, most solutions are still "very FDA-driven" and

'Case For Quality' Finds Home In 'Super Office'

FDA announced in late September that it's building a new "super office" within CDRH that will essentially dissolve and replace the Office of Compliance, ODE, and the Office of Surveillance and Biometrics. *(Also see "'Super Office' To The Rescue: FDA's Device Center Is About To Undergo A 'Total Product Life Cycle' Makeover" - Medtech Insight, 29 Sep, 2017.)*

Bill Maisel, the agency's deputy center director for science (and two additional FDA "acting" titles) will lead the new "Total Product Life Cycle" office, which will bring pre- and post-market experts together to provide the agency with better visibility of products, device-makers and various device classes from cradle-to-grave to help guide its pre- and post-approval decision-making.

In that TPLC super office, "Case for Quality will go under a structure we call 'Strategic Initiatives,'" CDRH Director Jeffrey Shuren said. "So, it will be driven at a very high level, and it will continue with me as the executive champion.

"Ultimately our goal is that [Case for Quality] becomes operationalized and it's incorporated into the DNA at CDRH – that it simply becomes day-to-day business," he added. "And, as we move forward, we will continue to have dedicated resources" for Case for Quality.

"very FDA-centric" – and "it's FDA ultimately making the call" anyway, Shuren said.

But through a collaborative community, a variety of stakeholders – both in the public and government arenas – can have a say in developing solutions that address specific needs.

"That is the mindset where we have been going – we're willing to make changes not simply because it's of value" to FDA, Shuren said. "Maybe it's not the most important thing to [the agency], but it is important to others that are out in the community. It's worth doing that because it pays off dividends for all of us."

The question is, he said: "Can we drive within Case for Quality … that kind of collaborative community, where FDA is not the one driving it? Where it's not FDA-centric, but we simply have a seat at the table as a member of the community, and are willing to engage in that give-and-take?"

By launching a collaborative community for Case for Quality, best practices could be developed for "new tools and methods" that would promote quality practices, Shuren said, pointing out that it would "ultimately get us to a continuous learning system where … we're identifying those practices and tools and methods."

And then, "let's assess and identify what works and what doesn't work through real-world experience, and then feed that back into the system," he said.

"So, that's what we're trying to achieve with Case for Quality. That is, in fact, the reimagining of the system."

SHUREN TOUTS CMMI PILOT

Arguably the most ambitious Case for Quality work to date is designs to launch an FDA pilot program in January that will gauge the manufacturing maturity of device manufacturers.

Under the Voluntary Medical Device Manufacturing and Product Quality Program, the quality systems and manufacturing processes of participants will be evaluated by third-party appraisers against the Capability Maturity Model Integration (CMMI) appraisal framework.

Results of a manufacturer's CMMI assessment will be shared with FDA; the agency will then use the information to help shape its regulatory, compliance and enforcement decisions. *(Also see "Quality On The Brain: FDA Maturity Pilot Aims To Shift Industry's Compliance Mentality To A 'Quality Mindset'" - Medtech Insight, 29 Sep, 2017.)*

FDA is aiming to accept at least 30 companies for the pilot, which will run during all of 2018. *(Also see "FDA Looks For Diverse CMMI 'Maturity' Pilot Enrollees; Device-Makers Expect Big Savings" - Medtech Insight, 16 Oct, 2017.)* Firms that take part will qualify for incentives such as waived pre-approval inspections and leeway on 30-day notice manufacturing-change submissions. *(Also see "Gifts For Industry: From Waived Inspections To Pre-Market Leeway, US FDA Woos Firms For Maturity Pilot" - Medtech Insight, 25 May, 2017.)*

"We're kind of saying, if you've gone through this appraisal and you rate very high on the maturity model, there are things in the FDA that we [can do to] help incentivize," Shuren said. "So, that will include opportunities for us to not conduct a pre-approval inspection [and to also] streamline 30-day notices. [Because] by the 30th day, there might have been multiple changes. So, let's package that together. Let's have a much more streamlined submission. And then we would do a review in about – here's what we're targeting – two business days."

In return, FDA would conduct a "quality check … by doing periodic audits of those submissions. We really want to make this work less burdensome for everybody, and better target our resources," he said.

"Why modify our submission review? Well, we want to build an environment of trust – trust between FDA and industry – and then leverage that trust and sort of drive greater transparency on the part of manufacturers where essentially they're opening their operations up more but they're doing it in a much safer way," Shuren said.

"Ultimately what we're looking for is value to patients – that we have better product out on the market, and we're rewarding those companies that have that greater focus on quality."

Published online 11/15/17

FDA Beefs Up Its UDI Direct-Marking Preferences In Final Guidance

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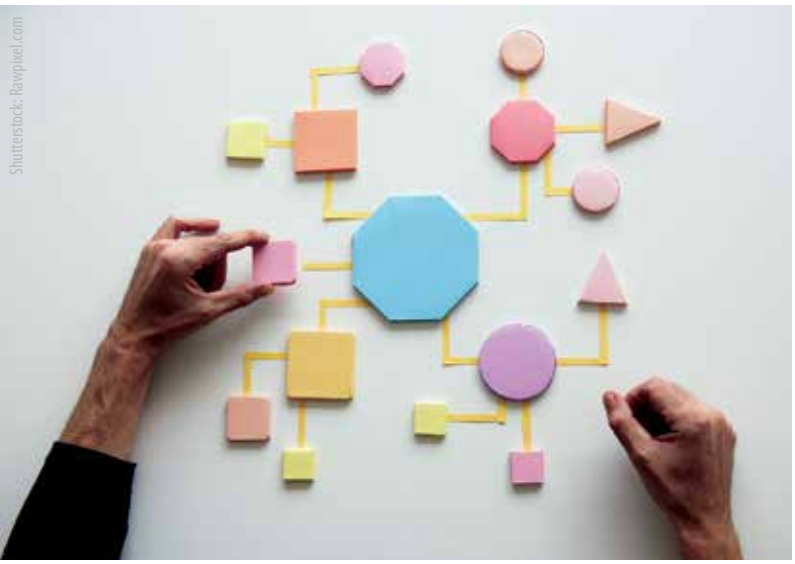

US FDA has clarified its preferred approaches for sponsors to take in directly marking Unique Device Identifiers on medtech products in a final UDI guidance released Nov. 16.

The guidance specifically addresses the agency's expectations for devices that must have a UDI marked directly on the product, in addition to having the identifier be included on labeling and packaging. Only devices that are intended to be used more than once and be processed before each use are subject to direct-marking requirements, according to FDA's 2013 UDI regulation. This does not include implantable and single-use devices.

Some sections in the final guidance have changed since the draft guidance was released on June 26, 2015. *(Also see "Direct-Marking UDI Draft Lays Out Tips, Timelines For Reprocessed Devices" - Medtech Insight, 25 Jun, 2015.)* Among these is section on devices that are consigned or loaned before the compliance date for class III devices, and the compliance date for class II devices.

In these cases, FDA says it recognizes that some devices might be consigned or loaned to hospitals or other health-care facilities prior to some of the applicable UDI compliance dates. To the extent those devices are required to comply with UDI regulatory requirements for labeling, direct marking or data format requirements, "FDA does not intend to enforce compliance with such requirements for those devices," the agency wrote.

The agency also updated a section detailing under what circumstances the agency will not enforce requirements for product identifiers.

GENERAL DATES FOR COMPLIANCE

Higher-risk devices that can be reprocessed are already subject to direct-marking requirements under the UDI rule's enforcement timeline, and the new guidance does not change any compliance dates. Life-sustaining and life-supporting devices – regardless of class – should have been marked with UDIs by Sept. 24, 2015; class III devices and those licensed under the Public Health Service Act were to have been marked by Sept. 24, 2016. Meanwhile, qualifying class II devices must be directly marked by Sept. 24, 2018, and class I and unclassified products by the same date in 2020.

For qualifying devices that are manufactured prior to their compliance, the guidance retains a three-year exception, based on the compliance date for UDI-labeling requirements, rather than the direct-marking compliance date. For example, the compliance date for class II devices that are not implantable, life-sustaining or life-supporting is September 2016, but if a device was manufactured and labeled on May 1, 2016, then it is not required to be UDI-labeled or -marked until Sept. 24, 2019.

MARKING FOR LIFE OF DEVICE, AND PRODUCT IDENTIFIERS

FDA has also added more language and explanation in sections specifying methods to directly mark a device. It expects the direct-mark UDI to last throughout the expected service life of the device, taking into account expected usage and reprocessing, according to the manufacturer's instructions. Among the marking methods permitted are etching, attaching a permanent plaque to durable equipment, or affixing a permanent tag, such as a radio frequency identification (RFID) tag to the device.

However, with some durable medical equipment, "a labeler will attach to the device hardware exterior a sticker or other item that displays information and is designed to last the expected service life of the device." As long as the item includes the UDI, "you have fulfilled the requirements," FDA stated.

Previously, FDA said the records do not need to list each individual UDI, meaning the device identifier plus the production identifier.

However, under the final guidance, the agency writes: "The records should be updated when changes to the production identifiers (PI) are made (such as lot or batch, serial numbers or expiration date), in order to reflect all PIs currently associated with each DI."

FDA also says that the Device Master Record must include or refer to the location of the DI for each particular version or model, "as well as each associated type of PI."

PERIODICALLY REASSESS USE OF EXCEPTIONS DUE TO NEW TECHNOLOGY

The agency acknowledges that sometimes it is not technologically feasible to mark a device, and it allows exceptions for these situations. FDA expects the labeler to document any rationale for the technological infeasibility. However, there will be advances in

marking over time, FDA states, and thus, "labelers should periodically reassess their use of those exceptions."

FDA also notes that sometimes the production identifier could be unknown when a device is being marked, so the agency says it "does not intend to enforce the requirement that the UDI, directly marked, include that production identifier."

The agency also reminds manufacturers: "Whenever there is a change to the device that results in a new model, a new DI must be assigned to the device."

REPROCESSED DEVICES USED BY ONE PERSON

Finally, FDA adds clarification its definition of devices intended to be reprocessed, and under which circumstances they must be marked.

If the device is intended to be used more than once, for different patients, than it must be marked. However, "if the device is intended to be used more than once by the same patient," even if it reprocessed, "then the device does not need to be directly marked with a UDI," the agency states.

In these cases, and in other situations when a company is requesting a specific alternative to direct marking, company personnel should carefully read the UDI regulations "and submit a request to FDA." If so, the agency "may grant an alternative to UDI direct-marking" that would provide for "more accurate, precise or rapid device identification," it said.

Published online 11/16/17

Germany's Medica 2017 Kicks Off Amid Changeable Outlook, As MDR Clouds Scud Into View

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One month after Germany's hung-Parliament general election, and with a new government still to be formed from the limited available coalition opportunities, the 19th German Bundestag sat in late October for the first time. Given the ongoing national leadership vacuum, federal President Steinmeier asked Chancellor Merkel and officials from her previous cabinet to head up executive decision-making for as long as it takes to form a new administration.

Seen from afar, the political management of Europe's leading economy – and medtech economy with sales of €29bn ($33.8bn) in 2016 – might seem almost tranquil, especially in view of the evident tensions in several other leading economies that have their administrations in place. A tongue-in-cheek survey run by the Opinion Control market research group, reported this week by the German website *Der Postillon*, revealed that 92% of the public are in fact happier without day-to-day government oversight, and evidently can wait longer for the anticipated Jamaica coalition. *(Also see "German Vote 2017: Business Must Wait As Limboland Merkel Faces Hard Coalition Choices" - Medtech Insight, 25 Sep, 2017.)* Precisely when it will be formed is anyone's guess.

Meanwhile, life goes on. The German medtech sector, which last week forecast industrial growth (domestic and overseas sales) of 5.9% in 2017, is looking to ensure that the industry exploits the shifting trends in health care and is in a position to advance the patient-centered innovation that the market is demanding.

THE ERA OF BEING 'BIG DATA SMART'

The biggest of these trends was broached in the run-up to Medica's Health IT Forum by Professor Andreas Pinkwart, minister for the economy, innovation and digitalization in the state of North Rhine-Westphalia. Medica runs from Nov.13-16. The benefits of integrating artificial intelligence (AI) into health-care delivery and R&D – already happening in the diagnostics field – are "promising," but the sector must become "Big Data Smart," he told *Medica Magazin*, including in areas like regen med for the heart, skin and lungs.

A looming issue – how to manage patient data security - needs to be understood and tackled if potential medical advances are not to be rendered inaccessible by ethical concerns. Society must decide quickly where and how big these barriers to progress are to be erected, as the patient becomes more in control of his or her own care.

At the same time, while AI and robotics are increasingly important parts of the ever-evolving medical sector, responsibility for the delivery of health care must not be taken away from medical care professionals, he said.

EU'S MDR IS A CONCERN FOR MOST

Other hurdles, like slow reimbursement and strict – maybe inappropriately so – regulation, serve to put the brakes on innovation adoption. The EU Medical Device Regulation (MDR) is making market access harder for breakthrough innovations, and Pinkwart speaks for many in urging more support mechanisms for SMEs, and firmer guarantees that sickness funds will adopt and reimburse new examination and treatment methods (NUBs). Similarly, a proper framework for health-care digitalization to ensure innovation continues to thrive and industry remains competitive is called for. A problem at present is that, at industry level, only 39% of Germany medtechs say they are "digital ready."

The German medtech industry sees the MDR and its associated higher market access costs as equally at the top of their list of burdens, along with the excessively long use/benefit evidence generation procedures demanded by the reimbursement authorities. "We want the new legislation period to find time to improve and speed up the medtech benefit-evaluation process," said BVMed chief executive Joachim Schmitt.

GOOD AND POTENTIALLY BAD MEDTECH OUTLOOK SOUNDINGS

Schmitt made this renewed call as he announced the findings of the association's autumn 2017 survey of members' views of the health and outlook of the industry. In the survey, 106 companies shared their views, which helped BVMed to paint the following relatively upbeat soundings:

- German medtech revenues are growing faster in international markets than on the domestic market (+2.8%);
- 26% of local companies have increased the investment in their business, in the face of persistent price pressures. 50% have maintained year-on-year spending growth;
- 29% spent more on R&D and 45% maintained previous levels of spending. German medtech companies' R&D levels average 9%; and
- Cardiology is the most innovative medtech sector in Germany, as voted by 36% of those polled, followed by oncology (29%), neurology (29%), diagnostic (27%) and orthopedics (16%).

While positives can be drawn from the survey, the pressure is still on companies working in Germany and serving the EU market.

Indeed, BVMed's Innovation Index has dropped to 4.5% from 6.2% a year earlier, due principally to concerns that the MDR will put a big squeeze on manufacturers. Of companies surveyed, 65% see the MDR as the biggest cloud on their economic horizon, and 63% specifically name the increased demand for clinical data as potentially financially debilitating.

In addition, 66% believe products will be withdrawn from the market on economic grounds, and two thirds think MDR-associated costs will rise. Only 44% (down from 66% in 2016) say they will increase staffing levels in the coming year.

Industry is aware that these messages won't be missed by the incoming administration and will clearly be hoping for business-friendly support from whomever is installed in the key roles.

Published online 11/14/17

Combining EU Notified Body MDR/IVDR Assessments: Can It Speed Things Along?

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There is an urgency in the EU medtech sector to have notified bodies designated under the new Medical Device and IVD Regulations (MDR and IVDR) as soon as possible because of the vast number of products that need to be reassessed under the regulations – many within the next two-and-a-half years (MDR) or four-and-a-half years (IVDR).

Many have speculated that notified bodies will be designated against the MDR first, followed by IVDR designation because of the different deadlines for compliance.

But even though the deadline for compliance with the IVDR comes in May 2022, two years after the deadline for compliance with the MDR, notified bodies applying for designation under the IVDR can start filing applications with the designating authority at national level at the same time as the under the MDR.

Indeed, there is no apparent difference in how the European Commission will be prioritizing the applications, it appears, based on a just-published Commission statement.

The Information note on joint assessments under the new regulations on medical devices says: "As of 26 November 2017, under one or both regulations, any conformity assessment body already designated under the Medical Devices Directives or any new conformity assessment body may submit an application for designation as a notified body to the responsible authority in a member state".

Does this mean that notified bodies will be able to be jointly assessed under both regulations? This is a key question given the huge workload that the Commission and the member states have ahead of them in auditing all the candidate notified bodies under the new regulations. The process will include joint audits, which will require the Commission and two member states to interface their calendars.

Shutterstock: Evgeny Prokopyev

The longer the process takes, the longer it will take for companies to be audited by notified bodies under the new regulations, an issue of great concern to the sector, given the number of devices that need to be audited and the likely drop in numbers of notified bodies and auditors under the new regulations. *(Also see "More EU Notified Bodies Bite The Dust" - Medtech Insight, 17 May, 2017.)*

The European Commission notes that there could be some possibility for efficiency in terms of joint auditing against both

regulations. The majority of the IVDR and MDR texts are very similar in nature, so it might make sense, from a resource standpoint, for the assessments to be carried out alongside each other, in cases when the joint assessors have the necessary experience and qualifications. But in practice, it is not clear how often this will be possible and clarification is needed from the European Commission.

The joint assessments under the MDR and IVDR will require different qualifications from the joint assessment team experts. As a result, two different on-site assessments will be required. But, the Commission says, "For the sake of efficiency, every effort will be made to ensure both on-site assessments are organized at a reasonable interval, so that the information collected during the first assessment can be used for the second one."

NO COMBINED JOINT ASSESSMENT

But as notified bodies must become designated under the new MDR and IVDR, they also must continue work under the existing medical device directives. Is it also possible to perform assessments in parallel under the medical device directives and the new regulations as a strategy to lessen the predicted logjam in notified body applications under the old and new frameworks?

To a limited extent, yes this will be possible. Certainly, the European Commission acknowledges that such an approach "could contribute to an efficient use of the resources available to those involved in the designation process."

But the Commission says that it is not possible to conduct a combined designation procedure under the medical device directives and the new regulations, which includes a combined joint assessment. This is because the respective designations have a different legal basis and, accordingly, are subject to different legal requirements. This means the processes and outputs are different in terms of deadlines, reporting, and consultations, it says.

The good news is that on-site assessments for each respective procedure could theoretically take place at the same time and include a review of the similar supporting documentation, while the respective requirements and steps of each designation procedure under the relevant legal framework will need to be followed.

The European Commission says it is mindful of the resources issue, and "aware of the challenges posed by the new regulatory regime." In line with its commitment to facilitating the smooth implementation of the two regulations it has been intensively preparing for the transition, including providing the guidance and training needed to secure a sufficient number of qualified national experts.

SHOULD NBS BE ASSESSED UNDER MDR OR IVDR FIRST?

Medtech Insight notes that, from one point of view, it would seem to make sense that notified body applications under the MDR are prioritized because of the earlier May 26, 2020, deadline and because there are significantly more medical devices than IVDs on the EU market – 500,000 compared with 40,000, according to European Parliament figures. (*See table above.*)

But, it is also worth remembering that the percentage of medical devices that may be able to benefit from the extended transition period (because they continue to be compliant under the medical device directives and there is no change in notified body arrangements) will be considerably larger than the percentage of IVD manufacturers, many of whom will need involvement of a notified body for the first time and will need to comply by the date of IVDR application on May 26, 2022, and no later.

And if the focus is entirely on devices at the beginning of the transition period and the notified body system gets clogged up working on devices, then this could have a major impact on the possibility for IVDs to be assessed on time for the May 2022 deadline. This is especially the case given the steep learning curve ahead for notified bodies and IVD companies alike, as they adjust to the new stricter classification and conformity assessment system and, for many, the need to work together for the first time. So, the numbers game is not entirely straightforward.

Devices Vs. IVDs: An EU Market Comparison

	DEVICES	IVDS
Products on the market	500,000	40,000
EU companies	25,000	3,000
People employed	575,000	75,000
Percentage that are SMEs	95%	95%

Source: European Parliament

The European Commission says it is mindful of the resources issue, and "aware of the challenges posed by the new regulatory regime."

Published online 11/20/17

'Old-Fashioned' Medical Device Regulation? New Regulatory Regime For EU Medtech In Wings

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The EU's medical device directives and new regulations form part of an "unnecessary and old-fashioned way of regulating that involves putting too many rules in the law." That is the view of Christopher Hodges, Professor of Justice Systems at the University of Oxford, UK.

Hodges, a well-respected legal scholar, believes the medtech sector can pioneer a more ethical, holistic and overarching way of regulating. Its known as Ethical Business Regulation (EBR) through European Business Practice (EBP), which, he envisions, could lead to a reduction in the weight of current rules.

EBR is of potential value to most sectors, and globally. Indeed, airlines already use a similar model with success, governments and councils can benefit, and organizations in countries as far afield as Australia are particularly interested in this new regulatory practice model.

But Hodges is no stranger to medtech – he began his now illustrious legal career in the sector. And he says that steps are being taken so that evidence from ongoing pilot studies in other sectors will be brought together to create a customized model for the medtech sector to trial.

There have already been discussions between the UK's Medicines and Healthcare products Regulatory Agency (MHRA), the British Healthcare Trades Association (BHTA) and the Association of British Healthcare Industries (ABHI) on this subject.

HOW EXACTLY DOES EBR WORK?

EBR is a generic concept and, at first, it is not straightforward to understand exactly how it would be applied. It is not intended, in the medtech sector, for example, to replace sector-specific regulations such as the medical device directives and the new Medical Device and IVD Regulations.

> "It will always be important to consider evidence over time and to note the direction of travel, such as whether improvements are being made," Christopher Hodges says.

Instead, it is intended to drive company culture which, if it works, will mean the need for less outside intrusion and enforcement, and, ultimately, fewer detailed regulatory rules.

Companies will need to demonstrate transparently, both within their own organizations and to external parties, that they take a truly ethical approach to compliance in their sector.

For medtech, this would mean a responsible and responsive implementation of the medical device directives, or the MDR and IVDR, for example, as well as all other relevant EU regulation relating to the environment, data protection and more.

All of this would need to be documented, feedback and surveys would need to be taken internally of employees, externally of suppliers and customers, including to ascertain whether the managers of an organization can be trusted to operate in this ethical dimension and to continually learn from mistakes.

LEARNING FROM MISTAKES, AND COULD PIP HAPPEN AGAIN?

In the long-term, Hodges is convinced that EBP will result in a "thinning out of quite a lot of rules." A significant part of what is in laws could then be in guidance, he told *Medtech Insight*, or in best practice. This, he says, would support more innovation.

"We definitely have an educational and communication challenge ahead," he admitted, "but we know the approach works."

One of the underlying principles of EBP is that organizations can be trusted to operate on the basis of EBP even if some things go wrong.

"It will always be important to consider evidence *over time* and to note the direction of travel, such as whether improvements are being made (in which case the organization should be encouraged) or not," Hodges said. He added that society must expect you to fail sometimes, but to keep learning through engagement. This, he explained, will encourage innovation.

Such a culture will encourage transparency and ensure colleagues are not fearful to admit mistakes.

So, if such an ethical culture pervaded the medtech sector, could we be confident that we would avoid a recurrence of an event like the PIP breast implant scandal, where the French company replaced medical grade silicone gel with industrial grade in its implants and remained undiscovered for years?

Hodges is convinced that at least some staff at Poly implant Prosthèse were aware of the substituted gel and that they should have felt empowered to

The Checklists

Hodges has co-authored a book with colleague Ruth Steinholtz, an international values-based business ethics advisor and founder and managing partner of law firm AretéWork, which will be available in December. It is entitled *Ethical Business Practice and Regulation: A Behavioural and Values-Based Approach to Compliance and Enforcement*. The book features an annex, which contains two suggested checklists to support EBP and EBR.

MHRA, BHTA and ABHI are now looking at generic lists to customize them for medical devices. Obviously, the application will need to be different to reflect the different risk classes of devices, Hodges explained, because of the involvement or not of notified bodies. And so, this would need to be worked through and applied in a customized EBR.

One of the suggested checklists in Hodges' book is a list of general questions that leaders of organizations might ask t to enable them to support EBP. The other suggested checklist is a list of the types of evidence that external stakeholders might take into consideration in making their judgement as to whether an organization can be trusted.

Questions from the first list include:

- Are we producing constant reliable evidence that the organisation itself can be trusted?
- What training are we doing to develop people's ethical awareness and facilities, including their ability to spot an ethical issue, analyse it properly and implement their decision?
- Are we developing a sense of internal cohesion, involving everyone across the entire organisation?
- Do we have enough and appropriate resources to support our people to identify and do the right thing?

When it comes to the types of evidence that may be provided to support ethical business practice and ethical business regulation, there is a separate, long list that includes:

- Evidence demonstrating an understanding of the fair and legitimate needs of all internal and external stakeholders, and of discussing, agreeing and reviewing how these may fairly be achieved.
- A written code of Ethical Business Practice, developed from within, based upon the organisation's values and aligned with the culture, forming the cornerstone of the organisation's approach to ethics and compliance.
- Evidence of tolerance for, and encouragement of, constructive conflict without fear of reprisals for raising difficult issues.
- Performance management systems and incentive schemes that reward good leadership and ethical behaviours, not just results, and that do not foster unethical behaviour.
- Evidence of supporting the adoption of EBP amongst stakeholders, including staff, suppliers, customers, regulators, local communities and society. Evidence that entities understand their supply chain. The extent of due diligence and engagement in EBP will depend on the level of risk and resources available to the parties. A higher-level example would be requiring and supporting suppliers to adopt ethical values and support structures, and to provide evidence of this.

raise the issue, but were deterred by the company's culture.

Whatever the case, the proposal raises the question of whether a more ethical and transparent culture would make more inroads into preventing a recurrence of situation like that with PIP compared to the huge hike in regulatory demands being introduced through the new EU MDR and IVDR. The PIP scandal was one catalyst for reforms moving forward in Europe, but, many have noted, the scandal was caused by fraudulent behavior, which can always go on, whatever the regulatory regime, in cases when people are clever enough to hide it.

Moreover, Hodges emphasized that the problem with overly prescriptive and punitive regimes is that they tend to scare people into keeping silent when there are problems. If so, *Medtech Insight* notes, it is perhaps no surprise that the worst of the health scandals that have occurred in the EU over the last decade – PIP and the Mediator drug scandal – have happened in France, the country which has arguably been the most heavy-handed in its enforcement policies, and in sharp contrast with the UK's "light-touch approach."

ARE YOU ON BOARD?

At the moment, the EBP approach still seems very theoretical to those accustomed to focusing on words and regulations. EBP needs to be seen as holistic, overarching, and something that encompasses the regulatory approach within an ethical structure, Hodges suggests.

The rub is that it could initially mean yet more work for companies, just at a time when the new regulations are overwhelming the sector. This could result in some resistance.

But Hodges message is that the sooner companies get on board with this, the sooner they will see the benefits for their companies in terms of innovation, reputation, sales and, ultimately, less rules imposed from outside. So, who is on board?

Published online 11/15/17

CONTINUED FROM PAGE 1

In 2016, about 563,000 procedures were done in the US with the da Vinci, with an estimated 44% involving gynecology procedures, 33% general surgery and 19% urology. Outside of the US, about 190,000 procedures were performed with the da Vinci systems, predominantly in urology. (See Table 1.)

The company says that more than four million minimally invasive surgeries have been performed with the da Vinci systems since 2000. In the Q3 2017 earnings call in October, Calvin Darling, senior director of Intuitive, said the company is increasing its estimate for 2017 from an estimated 14% to 15% above the approximately 753,000 procedures done in 2016 to a new range of 15% to 16%. In Q3, the company placed 169 systems vs. 134 systems in the same quarter in 2016.

The company's devices are used in all top-ranking US hospitals for applications predominantly in cancer, urology and gynecology. To increase MIS penetration, Intuitive and other manufacturers target specific procedures, geographies and physician specialties where MIS penetration is low and robotics could enable greater open-to-MIS conversion.

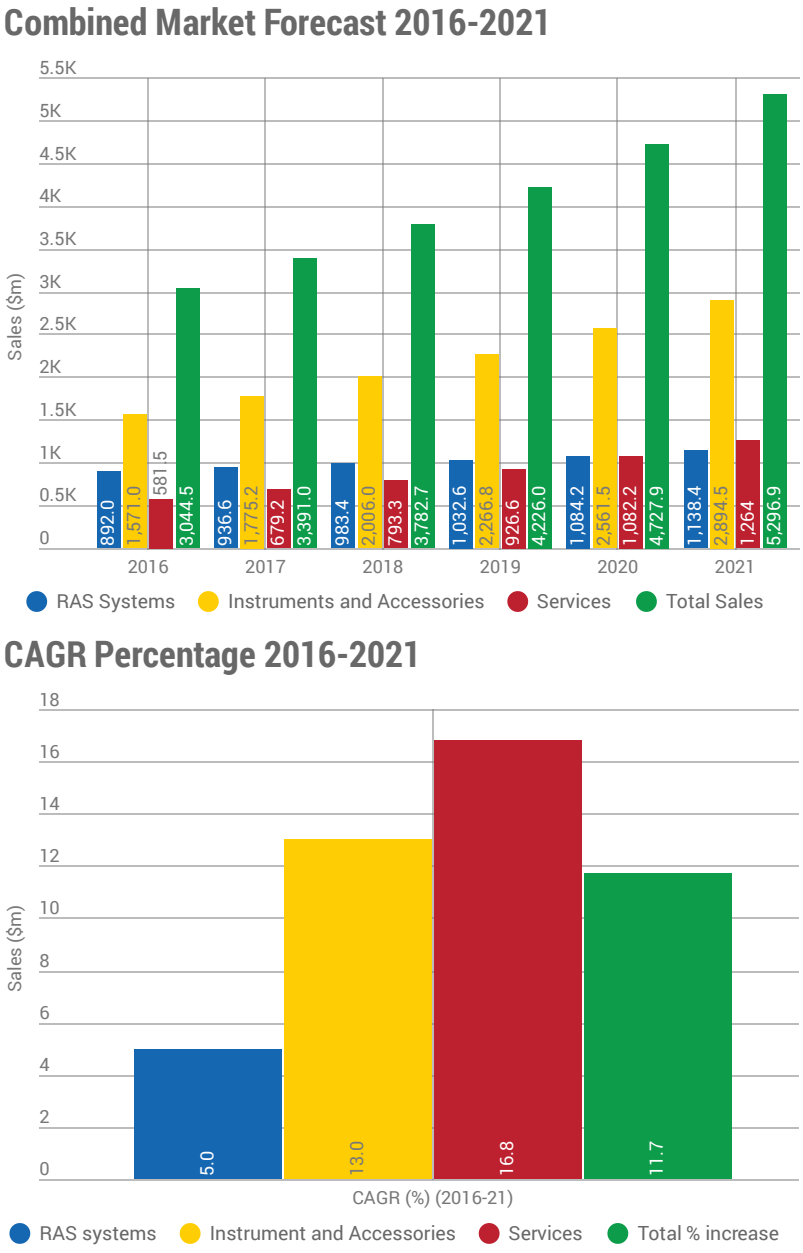
Intuitive's president and CEO, Gary Guthart, told investors during the Q3 earnings call that worldwide procedure growth was 15% in Q3 2017 compared to Q3 2016.

"As we have described on prior calls, we expect growth in general surgery and countries outside the United States to continue to lead performance while procedure growth in mature categories in the United States temper," Guthart said. He added that during the last quarter, Intuitive saw strength in general surgery in the US with moderate growth in the mature areas of urology and gynecology.

"Drivers of growth include US inguinal and ventral hernia repair, colon and rectal surgery and thoracic surgery as well as urology and gynecology procedures outside the United States," he said. "Procedure performance in Asia showed continued strength with solid growth in China, Japan and Korea. Overall European procedure growth moderated slightly from its first half of 2017 performance with trends varying by country."

FIGURE 1

Robotically Assisted Surgical Devices, Global Market Forecast ($m), By Revenue Segment, 2016-2021



Figures for RAS systems revenue include both leased and purchased systems. Totals may not sum due to rounding
"Robotically Assisted Surgical Devices Market," Meddevicetracker

The company is now on its fourth-generation system: the *da Vinci Surgical System Xi* has advanced instruments and accessories that target more complex procedures. The lower-priced models include the *daVinci X*, released in April 2017 as a valuable-based, upgradeable system, the three-arm *daVinci Si-e*, the refurbished *da Vinci Si* and Single-site instruments.

A potential game changer, according to industry insiders, could be the *da Vinci Sp* (single-port), which is expected to complete patient enrollment in surgery for clinical trials taking place in the US and Asia this quarter. Cases in Asia include transoral, urologic and colorectal surgery while those in the US focus on transoral surgery.

TABLE 1

Intuitive Surgical's *da Vinci* Surgery Systems Procedure Volumes, By Clinical Application And Geographic Area, 2016

GEOGRAPHIC AREA	CLINICAL APPLICATION	TOTAL	SHARE OF US TOTAL (%)
US	Gynecology	247,720	44
	General Surgery	185,790	33
	Urology	106,970	19
	Other	22,520	4
	Subtotal	563,000	n/a
Outside the US	Urology	190,000	n/a
	Total	753,000	n/a

General surgery includes bariatric, colorecal, cholecystectomy, hernia repair procedures. Most procedures outside of the US were in urology.
Source: Intuitive Surgical, 2016

Catherine Mohr, Intuitive's VP Of Strategy

Singularity University

Guthart said during the earnings call that Intuitive plans to file for 510(K) for the da Vinci Sp by year-end with follow-on submissions for more indications thereafter.

Catherine Mohr, Intuitive's vice president of strategy, told *Medtech Insight* what's exciting to her is that the Sp platform allows surgeons to do things they can't do with triangulation.

"This is where you start thinking about transoral and transanal, because you can come in through a natural orifice (such as the mouth) without having to stretch them out very wide to be able to get all the way down into the throat." In traditional surgery, surgeons often need to split open the neck.

She expects the instrument will have far-reaching applications.

"We're going for initial approvals in areas where we're kind of more experienced … but in the long run, I see a whole new set of different kinds of surgeries that are going to be enabled, because you can bring the instruments in in parallel," Mohr said. "It will be a long process to develop those procedures, to make sure that they're safe and effective, and to figure out how do we teach surgeons how to do a surgery they don't have an analog for."

But that's just one of many projects. Intuitive also recently made its way into early-stage lung cancer detection when it teamed up with China's **Fosun Pharma Kite Biotechnology Co. Ltd.** to develop a flexible robotic catheter that can navigate into the cavernous regions of the lungs.

As Intuitive continues to innovate, it's also facing rising competition (*(Also see "Intuitive Still Dominates, But New Robotic Surgery Players Could Speed Penetration" - Medtech Insight, 4 Aug, 2015.)*,.

Jennifer Grasso, director of Robotics and Emerging Technologies at **Zimmer Biomet Spine**, told *Medtech Insight* about 100 ROSA robots are currently used at sites in Europe, the Middle East, Asia Pacific and North America; six of these robots with spine applications are located in France, Germany, Belgium and Australia.

The vast majority of procedures have been brain-oriented. Asked about the marketing strategy for rolling out the combined ROSA spine and brain system in the US, Grasso said Zimmer Biomet will leverage its existing 50 "brain-install bases" in the US, mainly pediatric and academic hospitals, and other key sites. She said the company will swap out existing brain units with the combined brain/spine robots at institutions that have an interest in upgrading their robots.

Grasso declined to give an exact number for its spinal procedures. However, Zimmer Biomet will have a long way to go to catch up to Mazor, whose systems have been used in more than 24,000 cases worldwide.

"We've been working to combine the platforms for spine and brain together onto one platform, so we slowed the roll-out (in the US) until we can provide that," she explained. In other countries where

ROSA Brain is also marketed, the company will look at "procedure volume" to decide whether to swap out systems, she added. "It will be something that we will provide as an option," she said.

Among the newcomers in this space is Globus Medical's Excelsius GPS guidance and positioning robot, which was FDA-approved in August 2017 after receiving CE-mark approval in January 2017.

Asked what makes Zimmer Biomet's ROSA spine system different from others currently on the market, Grasso said they are very similar.

"There are some differences in imaging, compatibility, but for the most part they are very similar in providing an accurate trajectory for pedicle screw placement," she said.

Ronnie Mimran, a neurosurgeon with the Pacific Brain and Spine Medical Group in Danville, California agreed with Grasso.

Mimran said he's familiar with Zimmer Biomet's ROSA Spine and Globus Medical's Excelsius, but adopted the Mazor X for spinal surgeries eight months ago in his practice.

"For most types of procedures, they are very comparable in terms of what they can accomplish," Mimran told *Medtech Insight*. "The Mazor has the largest breadth of experience, however the Excelsius incorporates a navigation system, which gives us more features. You don't have that incorporated in the Mazor system, but the Mazor system is compatible with existing navigation systems."

Asked about his wish list for improvements, Mimran said that he'd like to see the development of more end effectors.

"Right now, the robots are good for trajectory guides for drilling and placing screws for other implants, but I'd like to see different end effectors that allow us to do more than that – drill, cut bone, perhaps a camera that can see around corners that we can't currently see."

Charla Fischer, a spine surgeon at NYU Longone Orthopedic Hospital, said she had an opportunity to test the Globus system and prefers it over current robotic systems available, citing ease of use and built-in navigation system.

"It combines the aspects of a robot, meaning it's got a mechanical arm that guides you, and it also has navigation, so on a monitor you can see in real time where your instruments are going in the spine," Fischer told *Medtech Insight*.

Ronnie Mimran, neurosurgeon

For brain surgeries, Mimran acquired a surgical robot developed by Toronto-based startup **Synaptive Medical Inc**. He considers this robot a real "paradigm shift."

The *Brightmatter technology* includes surgical planning and navigation, robotic digital microscopy and informatics. The information platform won FDA approval in early 2016, according to the company website.

"The Synaptive robot is different than the other types of robots," he said. "It helps surgeons visualize the anatomy better and allows for smaller incisions and smaller approaches, less tissue disruption and on the surgeon's side, less fatigue and easier visualization."

When it comes to robotic surgery for neurosurgeons, he said, "in the spine, the robot is sort of an incremental step forward, but in brain surgery, the Synaptive robot is a big step forward."

In the orthopedics space, robotic systems offer orthopedic surgeons better dexterity, efficiency in hand-eye coordination, ergonomic positioning and improved visualization with aid of computed tomography (CT) scans, preoperative plans and simulation software.

Several of the major companies have robots on the market, including Stryker's MAKO, which has a total knee application for use in conjunction with Stryker's Triathlon Knee (FDA-approved in 2015), and the widely used partial knee and hip replacements. In the third quarter of 2017, Stryker sold 33 Mako robots, up from 30 robots in 3Q 2016. Since the commercial launch of the Mako total knee application this March, around 9,400 procedures have been performed worldwide (Also see "Latest Mako Tech Fleshes Out Stryker's Robotic Joint Replacement Line But Cost Critics Still There" - Medtech Insight, 20 Mar, 2017.).

Stryker may soon face competition from Zimmer Biomet, which plans to launch a robot based on the ROSA technology for total knee replacement during the second half of 2018.

Smith & Nephew markets the *NAVIO surgical guidance* and positioning robot, developed by **Blue Belt Technologies Inc.**, for total hip arthroplasty and partial and total knee arthroplasty *(Also see "Blue Belt Robotic Surgery Buy Is A 'Must-Have,' Says Smith & Nephew" - Medtech Insight, 30 Oct, 2015.)*. Think Surgical markets the T*Solution One Surgical System* for total hip arthroplasty.

Among the emerging products in this space are Swiss-based **AOT AG's** CARLO, which uses laser, robotics and navigation systems for osteotomy and the University of Calgary's *neuroArm 2*, which is controlled by a surgeon from a computer workstation and works in conjunction with an intra-operative MRI.

Head, Neck, ENT

In the head, neck/ear, nose and throat segment, three companies have robotic-assisted systems on the market. They are Intuitive's da Vinci, Medrobotics' Flex Robotic System, which was CE marked in March 2014 and FDA-approved in July 2015 for transoral applications, and Renishaw, which markets the *Neuromate* stereotactic robot for electrode implantation, which is approved in the US and Europe.

WATCH

Go to http://bit.ly/2iGaZi9 to see Synaptive Medical's Brightmatter in action.

Cardiovascular

In the cardiovascular segment, several companies are on the market with robotic-assisted technologies that aim to provide surgeons with better control and precision while shielding them from radiation.

Auris Surgical Robots, which bought Hansen Medical in July 2016, gained rights to two catheter guidance and positioning robots: The *Sensei X2*, which is sold in Europe and the US since October 2014 and the *Magellan*, which became available in the US in 2012 and is also sold in Europe.

Catheter Precision (formerly Catheter Robotics) markets the *Amigo Remote Catheter System*, used for guidance and positioning of a catheter in electrophysiology procedures (EP) such as atrial fibrillation. The Amigo received the CE mark in 2010 and FDA (510K) clearance in August 2012.

Corindus Vascular Robotics' *CorPath System* was the first RAS system approved for use in PCI. The next-generation *CorPath GRX* debuted in the US in January 2017. Corindus seeks an indication approval for peripheral vascular procedures and believes the technology has applications in neurointerventional and more complex cardiac interventions such as structural heart applications.

Stereotaxis sells its *Niobe ES Magnetic Navigation* system for managing arrhythmia and coronary artery disease in major markets including Canada, China, Japan, Europe and the US.

Among the emerging technologies is the MRI-guided robotic intravascular catheter system for pulmonary vein isolation ablation to treat atrial fibrillation in development by Case Western Reserve University.

Thoracic

The market opportunity in thoracic surgery for minimally-invasive surgeries is significant and the proliferation of low-dose computed tomography (CT) scanning and other advanced diagnostics are expected to increase the potential population as more people are diagnosed in earlier, more treatable stages of disease.

Market leader Intuitive estimated that the market opportunity in thoracic is around 100,000 potential procedures, with the biggest opportunity being in minimally-invasive treatment of lung cancer.

Intuitive executives said last year that the company wants to expand into the thoracic surgery market and did so with the launch of the da *Vinci XiEndo Wrist* Stapler 30 and *XiSingle-Site* instrument and accessory kit, which received FDA 510(K) clearance in March 2016. The stapler is also indicated for use in gynecology, urology and general surgery.

According to *Meddevicetracker*, over the long term, the biggest market opportunity could be in countries where smoking rates are high, such as in Europe and Asia. Intuitive presented favorable first results of the flexible robotic catheter it developed with China's Fosun Pharma at the CHEST Annual Meeting this month, suggesting that the system is safe and a feasible approach to sample lung tissue.

Zarnegar said most major hospitals in the US already have adopted surgical robots and Weill Cornell Medical Center has six systems.

"It's used by select robotics specialists from different divisions," Zarnegar said. "I think when you do that, then there is an overwhelming advantage of the robotic technology, so I think that's where it starts paying off. It's all based on the number of cases and if you can maximize case utilization, then the original cost kind of evens out."

Mimran said for some health systems it makes sense, for others it may not.

"I think in general you're going to have fewer complications, overall less radiation to the surgical team and the patient, and shorter length of stay (hospitalization) because more surgeons will feel more comfortable doing more things minimally invasive and with that patients will have faster recovery," spine surgeon Charla Fischer says.

Auris Surgical Robotics received FDA approval in May 2016 for the *Auris Robotic Endoscopy System*, a patient-side system that is intended to provide bronchoscopic visualization of the patient's airways.

Also competing with Intuitive in this market segment is TransEnterix's Senhance system.

Both Medtronic and **Verb Surgical**, which is **Johnson & Johnson Medical Inc.'s** joint robotic surgical project with Google's **Verily Life Sciences LLC**, are also expected to rival Intuitive with their respective technologies in development. Verb Surgical's robot, which has thoracic, colorectal and oncology applications, is designed to be smaller, smarter and less costly with machine learning and advanced visualization components. It is expected to hit the market in 2020.

LIMITERS

Cost

The high cost of owning and operating robotic systems continues to represent a major barrier to entry, especially for smaller, low-volume hospitals.

"That's the same type of question every hospital and every spine surgeon needs to evaluate when it comes to a capital purchase and every institution and surgeon is different."

Fischer agrees that the high cost of installing a robotic system puts a damper on wider adoption of RAS, but she finds that in spine surgeries robots offer multiple advantages for patients, surgeons and hospitals.

"I think in general you're going to have fewer complications, overall less radiation to the surgical team and the patient, and shorter length of stay (hospitalization) because more surgeons will feel more comfortable doing more things minimally invasive and with that patients will have faster recovery."

According to Intuitive, in 2016, the average sales price of an Intuitive Surgical da Vinci system declined from $1.54m in 2015 to $1.52m. Per-procedure costs for the da Vinci ranged from $700 to $3,500, and system maintenance expenses ranged from $80,000 to $170,000 per year.

Although more systems are available at different price points, Intuitive customers

TABLE 2

Average Sales Price Of Selected Robotically Assisted Surgical Devices, 2017

COMPANY	PRODUCT	APPLICATION	PRICE RANGE ($)
Intuitive Surgical	da Vinci	Cardiothoracic surgery, general surgery, gynecology, head and neck surgery, and urology	550,000-2,500,000
TransEnterix	Senhance	General abdominal surgery (laparoscopy) and gynecology	1,800,000-2,000,000
Stryker	MAKO	Arthroplasty	1,000,000
Medrobotics	Flex Robotic System	Flex Robotic System	<1,000,000
Titan Medical	SPORT	General abdominal, gynecology, and urology	<1,000,000
Mazor Robotics	Renaissance	Brain and spine	849,000
Medtech/Zimmer Biomet	ROSA	Cranial and spine procedures	700,000
AKTORmed	SOLOASSIST endoscope holder	General surgery, gynecology, and urology	75,000
FlexDex Surgical	FlexDex instrument	n/a	500
Blue Belt Technologies/ Smith & Nephew	NAVIO	Arthroplasty	400,000-450,000

Source: "Robotically Assisted Surgical Devices Market," Meddevicetracker

continue to purchase the da Vinci Xi system over the less expensive and less capable Si models by a factor of about three to one, according to *Meddevicetracker*. *Meddevicetraker* expects that the level of growth in the RAS systems market is expected to be constrained due to rising sales of lower-priced systems.

These include Medrobotics' Flex Robotic System for head and neck and colorectal surgery and Titan Medical's SPORT product for general abdominal, gynecologic, and urologic indications, which may be launched by 2021.

But Mohr isn't convinced that surgical robots that are going to be commercialized will be less expensive than the da Vinci systems.

"I think they may discover they're very surprised at how much it actually costs them to run and support a robot program," she told *Medtech Insight*. She said when hospitals evaluate whether to invest in a robot, it's less about cost and more about value. "Does it bring enough value to justify the cost," she said. The move toward value-based and outcomes-based health care in Europe and the US will work well for Intuitive, she said.

Though, some industry insiders say that the jury is still out whether robotic surgery uniformly leads to better outcomes with studies offering varying conclusions.

During the Q3 2017 earnings call Patrick Clingan, Intuitive's VP of finance and sales operations, pointed to a recent economic analysis that studied the impact of da Vinci hysterectomy in Denmark, published in the Journal of Robotic Surgery. Comparing cost of care from the previous year to year following a hysterectomy for benign and malignant conditions in more than 7,600 hysterectomy patients across open, laparoscopic and da Vinci Surgery, the authors found in comparison to open and laparoscopic surgeries the da Vinci was less costly for benign procedures and more expensive for less complex malignant procedures. The authors concluded that "the use of robotic technology for hysterectomy is potentially cost saving from a broad health care prospective."

Another study published in the *Journal of the American Medical Association* in 2013 found that robot-assisted hysterectomy had similar complication rates as laparoscopic hysterectomy, but cost nearly $2,200 more per procedure.

While reimbursement rates for patients in the US tend to be the same whether they opt for robotic surgery or not, proponents of robotic systems say hospitals save money when they factor in shorter length of stay and lower complication rates for patients. But more peer-reviewed data is needed to show superior outcomes with RAS systems compared to open surgery or MIS.

Learning curve is often cited as another issue. But Mohr said it has a "fuzzy definition."

"What a lot of people talk about when it comes to learning curve is how many cases does it take them to get back to the same time that they were doing it before, but if you were to think about learning curve in terms of how many cases do you need to do before you've got better outcomes or before you've got fewer complications, the learning curves are actually very short," she said. Getting to the point when a surgeon feels confident or comfortable doing a robotic procedure can also vary and then there is the issue of complexity of a surgery.

Robotic surgery is undoubtedly the future. With increased demand by patients and expanded indications and technological advancements, more hospitals and ambulatory centers will adopt RAS. In the future, RAS systems will play a greater role in workflow and supply chain management of operating rooms with systems analyzing how much time a surgery will take, what instruments and implants are required and preorder supplies.

At Intuitive, Mohr will push for continued innovation.

"When I think about the role that robotics is playing … it's not just the robot as a set of manipulators," she said. "It's a platform onto which we can bring a lot of other technologies."

Published online 11/10/17

Exec Chat: How Verb Surgical Will Deliver On Surgery 4.0

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The advent of laparoscopic surgery in the 1980s heralded a new wave of surgical techniques – dubbed "Surgery 2.0" – that allowed for safer procedures and better outcomes compared to previous-generation open surgery. Robotic devices, led by **Intuitive Surgical Inc.**'s *da Vinci*, rang in Surgery 3.0, which allows even more precise and controlled procedures and, in turn, enables surgeons to treat ever tighter anatomical spaces and, potentially, more conditions. (*Also see "Ever Decreasing Dimensions, Snakes And Origami: The Next-Gen Surgical Robots" - Medtech Insight, 28 Feb, 2017.*).

Scott Huennekens discusses how Verb Surgical will deliver on Surgery 4.0 at the APAC Medtech Forum

Over the next few years, we will see yet another category of surgical solutions to address the limitations of today's robotics surgery and mark a new chapter – Surgery 4.0 – in this evolving sector. That's according to Scott Huennekens, who heads the firm that hopes to lead the charge.

This next generation of surgical innovation, called digital surgery, is not about incremental improvements to current robotic systems, but will bring in elements of advanced computing that other industries are already embracing, Scott Huennekens, CEO of Verb Surgical, told delegates at the Asia-Pacific Medtech Forum held Nov. 8 in Singapore.

Huennekens asserted that Verb, the joint venture formed two years ago between Johnson & Johnson's Ethicon and Google's Verily, is not a developer of surgical robotics device. Robotics is just one of the five technology pillars that form the company's digital surgery platform, he points out. The other four technological elements are: advanced surgical instrumentation, enhanced visualization, connectivity and data analytics & machine learning.

"The hospital operating room has not maintained the pace of capitalizing on digital innovation as with other areas of health care," said Huennekens. The introduction of surgical robotics might have its advantages over non-robotic surgical techniques like open or laparoscopic surgery, but there are also limiting factors, he stresses. In particular, the high cost of capital equipment and the large footprint of the systems, mean it still represents a very under-penetrated market – only 700,000-plus procedures have been performed using surgical robotics – and a very US-centric one to boot.

There are five billion people in the world who are unable to access surgical care and around 143 million surgeries that need to be performed annually. Low-skilled surgeons have three times more complication rates and five times the mortality rates compared to highly skilled surgeons, Huennekens pointed out. The vision for digital surgery is to build a smart system that applies machine-learning capabilities with semi- and fully autonomous features, and make the system smaller, modular, intuitive to use and cost-effective. The ultimate goal is to "democratize surgery" and globalize of the technology, the CEO said.

This won't happen immediately – it's more likely be 20-30 years down the line, Huennekens acknowledged. But, he says, companies like Verb are taking steps in the right direction. The company now has a working prototype of its digital surgery system and plans to launch it by 2020.

The first iteration of the platform will focus first on building capabilities that provide surgeons with actionable information via dashboards and reports. In an additional three-to-five years, it plans to introduce semi-autonomous features that leverage machine-learning and pattern-recognition capabilities, and, then, 7-10 years down the road, the system could boast autonomous closed-loop feedback features to provide even more guidance to the surgeons and ensure better outcomes.

Medtech Insight chatted with Huennekens following his APAC Medtech Forum presentation to find out more about the positioning of Verb in the vanguard of the digital-surgery movement, what his plans are for the company once it launches a product, and what lessons he learned from his prior experiences at other innovation-leading companies.

Medtech Insight: You made it clear in your presentation that Verb Surgical is a digital surgery company, and not a surgical robotics company. Do you think that message is getting through and the medtech industry is understanding that differentiation?

Scott Huennekens: You're right, people still bunch us with robotics. And at conferences, I say "no, we're going to speak last" because we're different from that Surgery 3.0 world – we do things and view things differently. We are going to deliver on [this new generation of] Surgery 4.0, but it doesn't exist

yet; we're creating a new category. We're beginning to talk about it and so is Medtronic. *[Editors' note: Medtronic is co-developing products in this area with Israeli company Mazor Robotics to combine respective expertise in surgical navigation and implant systems and surgical planning].*

Intuitive Surgical is a robotics company. It believes robotics is the solution, while we're saying, we are a surgery company and what are the best solutions to improve surgery? That could include robotics, machine learning, advanced visualization, data analytics, all those things are important. Some elements are more important for certain steps and cases, whether it's to improve outcomes or optimize costs. If you can do a step of a procedure with the same quality without a robot, don't use a robot, do it laparoscopically. But if something can be done with a higher quality and half the time, at the same cost, it's with the robot. Make the right decision – but it has to be always there and always on in order for you to do that.

With my prior [intravascular ultrasound] company, Volcano Corp., we integrated the system into every single lab and that's what we're going to do with Verb's technology. When it's always there and always on [rather than having to wheel it in each time], the economics change – the time to set up and use goes down dramatically. And because you're using the system, the procedure takes half the time and cost-per-case goes down.

> “Intuitive Surgical ... believes robotics is the solution, while we're saying, we are a surgery company and what are the best solutions to improve surgery? That could include robotics, machine learning, advanced visualization, data analytics – all those things are important," Scott Huennekens, CEO of Verb Surgical, says.

One very integral part of your digital surgery architecture is the cloud-connected surgeons' portal where they can share their experiences and also access data pre-, intra- and post-surgery and this portal will help deliver this end-to-end experience you want for the surgeon. Can you elaborate more on this and if there are any regulatory issues in terms of having to integrate these apps or its many other software components into your system?

Huennekens: It's an open platform. Just the same thing with Apple. You can put an app on an iPhone and make it a medical device. That software app to do your blood pressure and blood glucose monitoring has to get its own regulatory approval. The phone is agnostic. So, our system is agnostic – you can develop a software package that rides on it that does anatomic identification for a particular procedure, like a lap hernia, or specialized software that allows you to do it robotically better. So, there will be software made by third party software developers and they will have to get own approvals for those apps. You may have to work with the vendor to get access -- we would work with a third party to get it validated, like how Apple validates software that goes in its App store.

There are still a lot of people out there who view your technology as a "nice-to-have", rather than a "must-have." What's your response to those who question the accessibility of your digital surgery platform, especially for patients who are in resource-constrained Asia-Pacific geographies?

Huennekens: It will take time and scale of a market to allow you to drive costs down. Out of the gate, we will be focused primarily on the larger more developed markets but then we'll evolve into the other markets over time.

You did acknowledge that your vision of Verb Surgical "democratizing surgery" through its digital surgery technology won't happen overnight and it will take about 20-30 years to realize. So, if we were to break down the time period from now until then, into more bite-sized pieces, what are the milestones you've set yourself? You've already got a working prototype of your system and aim to launch it in a few years, by 2020. What are your expectations after that?

Huennekens: From the time of launch in 2020 or earlier, by 2030, our hope is that in any advanced economic first-world countries, 80% of their ORs have a digital surgery platform – whether it's with our system or Medtronic's or Intuitive's. And Surgery 4.0 should be well on its way at that point in time. It basically is going to future-proof that OR to allow you to do all the things to get that S-curve to continue and improve outcomes. And with more and more volume and capability, you will be able to drive costs down as well.

For example, in 1984, when I got my first IBM PC, I paid $3,000 for something that had a RAM of 286K and then, look, five years later, you can pay $1,000 for a lot more RAM and features. That's what's going to happen in robotics. Today, is the beginning of robotics across multiple industries [and] that's going to drive down all these manufacturing costs. The controls and brakes, all these elements will become cheaper and cheaper and you'll be able to make these robotic arms very inexpensively. And with an arm being inexpensive, everything else is going to be cheap. Ten years after our system is released, robots are going to be less than $100,000 per OR, and we're probably going to move towards most of them being provided free of charge and you upcharge on the instrument. If you go to a Cleveland Clinic, and they have 14 ORs, and they are doing $15m of disposable instruments, you're going to make sure they have your robots in each OR, so you can drive the disposable revenue. It's the razor/razorblade model. And as you go into the secondary and tertiary markets, the costs will be much lower and you can also bring in all the learning from the millions of procedures that have been done with your system.

You've got a long background in the medical device industry. You ran Volcano before selling it to Philips and you've also been involved with several other companies that you grew and took to the public markets. What are the most important lessons that you learned from your previous experience that you've found most useful when working with Verb?

Huennekens: Innovation in general is a mindset. A mindset of saying "things are not impossible." The grit, the persistence. One of my favorite sayings is, "There are no bumps in the road. That is the road." And there are going to be those when you innovate and creating what's next and you've got to figure out ways to overcome them. What I've found, whether it is Verb Surgical or Digirad [where I was president and CEO], or Endochoice [where I was chairman], you've got to be focused and have a small team built around great culture and have the best people who will figure out how to get it done.

Huennekens: Just do it?

Yes, it's not that hard. You want to sound smart but part of it is showing up and believing and doing it. I mean, how do you run a marathon? One mile at a time. It's the discipline to get up to train and work at it so that you can do 26 miles when race day comes. For a lot of startups, they might think "Jeez, that's a lot of work to try and achieve in five years" and it can be overwhelming for a lot of people, but for me, it's about breaking it down into small increments; tackle those small increments, drive them, get them done, celebrate after doing it, and then onto the next challenge.

The other thing to remember is change is the only constant. You see with a lot of startups where the founders fall in love with their idea. For me, it's not about the idea; it's about the success. So, with every startup I've been involved in, I've learned that you've got to change. You've got to be willing to adapt your business model, you've got to be willing to adapt your partners – if it makes sense to merge with something, buy something, who cares? The goal is success and this leads to another one of my favorite sayings: "I'd rather be effective than right."

Published online 11/14/17

Stryker's DAWN Thrombectomy Trial Could Also Help Medtronic And Penumbra

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Sales of mechanical thrombectomy systems are poised to get a boost from the published results of the DAWN trial, which showed outcomes for disability are better with thrombectomy plus standard medical care than with standard medical care alone in the subset of acute stroke patients who are treated six to 24 hours after onset and show a mismatch between the severity of the clinical deficit and the infarct volume.

"The DAWN data has already boosted the growth rate of the mechanical thrombectomy market," Wells Fargo analyst Larry Biegelsen writes in a Nov 12 note. He estimates that mechanical thrombectomy is used to treat only about 30,000 of the roughly 300,000 patients who could benefit from mechanical thrombectomy every year in the US, "which implies the market is very underpenetrated."

The DAWN results "should help further drive the penetration of mechanical thrombectomy for stroke because the DAWN study demonstrated that treating certain ischemic stroke patients who present later than the current guidelines recommend (between six–24 hours versus up to six hours today) can improve outcomes," Biegelsen explains.

Although DAWN only used **Stryker Corp.**'s *Trevo Retriever* thrombectomy system and Stryker "should disproportionately benefit from the trial," the DAWN results will also help sales of **Medtronic PLC**'s *Solitaire* and **Penumbra Inc.**'s *ACE 68* system, Biegelsen explains.

The results of DAWN (Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo), sponsored by Stryker, were published online Nov. 11 by the *New England Journal of Medicine*. Data from the trial were also presented at European Stroke Conference in Berlin in

May by Joint Principal Investigators Raul Nogueira from Emory University in Atlanta and Tudor Jovin of the University of Pittsburgh.

The trial was originally designed for 500 patients but was stopped in March – 31 months into the trial with enrollment of just 206 patients – after a pre-specified interim review showed DAWN already met its co-primary endpoints in favor of thrombectomy. *(Also see "Starts & Stops: Boston Scientific Starts, Stops, And Finishes TAVR Trials" - Medtech Insigh, 14 Mar, 2017.)*

The patients in the trial all had evidence of occlusion of the intracranial internal carotid artery, the first segment of the middle cerebral artery, or both, on computed tomographic angiography or magnetic resonance angiography assessed with automated software. To be included, the patients also had to show a mismatch between the severity of the clinical deficit and the infarct volume based on National Institutes of Health Stroke Scale. Also, all of the patients in the trial were known to be well no less than six hours before randomization into the trial, so the patients did not meet the usual criteria for treatment with intravenous alteplase, because they arrived at the hospital too late or because they had been treated with intravenous alteplase and still showed persistent occlusion.

The patients were randomized to treatment with Stryker's Trevo thrombectomy system and medical therapy or medical therapy alone and then stratified by the interval between the time elapsed since the patient was last known to be well – six to 12 hours or 12 to 24 hours – and the occlusion site – intracranial internal carotid artery or the first segment of the middle cerebral artery. The medical management in the trial was prescribed according to the latest professional guidelines for the country where the patient was treated, including antiplatelet, thrombolysis, and blood-pressure management drugs.

At the 90-day follow-up, the patients' mean score on the utility-weighted modified Rankin scale, a standard scale of stroke-related disability, was 5.5 in the thrombectomy group and 3.4 in the control group. Bayesian statistical analysis showed that the posterior probability that the thrombectomy group had a superior outcome is more than 99.9%, according to Nogueira and colleagues.

Stryker's Trevo Retriever

Trevo® XP ProVue Retriever
Image courtesy of Stryker Neurovascular

Also, at 90 days, 49% of the patients in the thrombectomy group were functionally independent compared to just 13% in the medical therapy-only group. The rates of symptomatic intracranial hemorrhage and 90-day mortality were similar in both groups. The authors also point out that the safety profile for thrombectomy performed six to 24 hours after the onset of stroke was similar to the safety profile for thrombectomy performed within six hours after the onset of stroke in previous trials, and that the rates of death and symptomatic intracerebral hemorrhage were about the same as the rates usually seen with standard medical care.

"Because our trial restricted enrollment to patients with infarcts of a small or medium volume, our findings may be concordant with previous reports that the extent of tissue injury is a determinant of the risk of symptomatic intracerebral hemorrhage after reperfusion therapy," the authors explain. "On the basis of retrospective studies, approximately one third of the patients with occlusion of a proximal anterior cerebral vessel who present within six to 24 hours after the onset of stroke may meet the imaging-based eligibility criteria that were used in this trial."

Although DAWN clearly establishes the benefits of thrombectomy for the subset of stroke patients enrolled in the trial, "further studies are needed to establish the prevalence of patients who would be eligible for thrombectomy among the entire population of patients with ischemic stroke [and] further studies are also needed to determine whether late thrombectomy has a benefit when more widely available imaging techniques are used to estimate the infarct volume at presentation, such as assessment of the extent of hypodensity on non-contrast-enhanced CT."

In an accompanying editorial, Warner Hacke, of the University of Heidelberg in Germany, writes, "The DAWN trial gives us hope that trials investigating the use of late intravenous thrombolysis that require the presence of ischemic tissue might have positive outcomes" including the ongoing WAKE-UP trial of MRI-based intravenous thrombolysis, the ECASS-4 EXTEND trial investigating the mismatch between diffusion-weighted MRI and perfusion MRI, the EXTEND trial of an automated method of perfusion CT, and the DEFUSE 3 trial of thrombectomy six to 16 hours after the onset of a stroke.

"These imaging-based approaches represent a new 'DAWN' for the selection of patients who are likely to benefit from thrombectomy that is performed far longer after the onset of stroke than current guidelines suggest, at least among patients who have severe stroke, vascular occlusion, and penumbral tissue," Hacke explains. "However, the results of the DAWN trial do not support a general liberalization of the time window for thrombectomy or thrombolysis. Reducing the time from the onset of stroke to treatment remains essential and results in the best outcomes. It is likely that a limited proportion of patients with occlusion of a large vessel who present late after the onset of stroke will have a small infarct core and a large volume of tissue at risk, as did the patients in the DAWN trial. For those patients, late thrombectomy works – but as of now, as far as we know, it works only for them."

Published online 11/15/17

Neurostimulator Is First Device Marketed To Reduce Opioid Withdrawal Symptoms

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FDA on Nov. 15 granted **Innovative Health Solutions, Inc.**, a *de novo* class II designation for the *NSS-2 Bridge*. The device is a percutaneous nerve field stimulator indicated for use to reduce opioid withdrawal symptoms, the first device to gain such an indication.

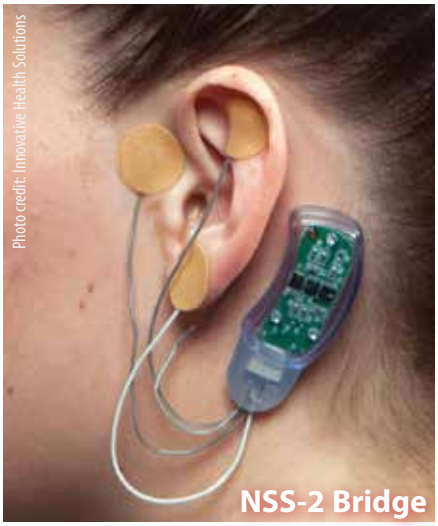
"Given the scope of the epidemic of opioid addiction, we need to find innovative new ways to help those currently addicted, to live lives of sobriety with the assistance of medically assisted treatment," commented FDA Commissioner Scott Gottlieb.

Gottlieb has been instrumental in pushing for more marketing authorizations of devices and drugs to treat opioid addiction, as part of an overall government-wide effort to address the opioid crisis. *(Also see "Five Takeaways From Commissioner Gottlieb's Talk At The National Press Club" - Medtech Insight, 6 Nov, 2017.)* "The FDA is committed to supporting the development of novel treatments, both drugs and devices, that can be used to address opioid dependence or addiction, as well as new, non-addictive treatments for pain that can serve as alternatives to opioids," Gottlieb said.

Lawmakers on the House Energy and Commerce Committee also applauded clearance of the NSS-2 Bridge. "The expansion of the NSS-2 Bridge is another promising tool in the collective fight to combat the opioid crisis," noted a statement from the committee, which has been holding a series of hearings on the opioid crisis.

Initially cleared by FDA in 2014 for use with acupuncture, the NSS-2 Bridge electro-auricle device would only be available by prescription, and is contraindicated for patients with hemophilia, those with cardiac pacemakers, or patients diagnosed with psoriasis vulgaris.

The *de novo* pathway is used for low- to moderate-risk devices that are novel and that have no legally marketed predicate device that can be used to show substantial equivalence.



STIMULATING THE CRANIAL NERVES

The NSS-2 Bridge is a small electrical nerve stimulator placed behind the patient's ear. It contains a battery-powered chip emitting electrical pulses to stimulate branches of certain cranial nerves. The stimulations may provide relief from opioid withdrawal symptoms that can include sweating, gastrointestinal upset, agitation, insomnia and joint pain.

To allow marketing of the device, FDA reviewed data from a single-arm clinical study of 73 patients undergoing opioid physical withdrawal. Study investigators evaluated patients using the clinical opiate withdrawal scale (COWS), an assessment conducted by a health-care professional that looks at symptoms including resting pulse rate, sweating, pupil size, gastrointestinal issues, bone and joint aches, and tremors and anxiety.

On the 0-36 COWS, the average score for all patients in the trial was 20.1, and results showed that all patients had a reduction in symptoms of a least 31% within 30 minutes of using the device. Further, 64 of the 73 patients (88%) were able to transition to medication-assisted therapy after five days of using the device.

FDA also said in its Nov. 15 notice on the device that it would be designated as class II with the establishment of special controls, and identified potential risks. Risks and mitigation measures are summarized in the table below.

Also, FDA specified that labeling for the device include a detailed summary of the device technical parameters, a warning stating that the device is for use on clean, intact skin, instructions for use, including placement of the device on the patient, and a shelf life.

Published online 11/15/17

NSS-2 Bridge

IDENTIFIED RISK	MITIGATION MEASURES
Adverse tissue reaction	Biocompatibility evaluation
Electrical, mechanical, or thermal hazards leading to user discomfort or injury	• Electromagnetic compatibility testing • Electrical, mechanical and thermal safety testing • Non-clinical performance testing • Software verification, validation and hazard analysis • Labeling
Infection	• Sterility testing • Shelf life testing • Labeling

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