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"In a constrained budget environment, industries that benefit from FDA's approval can and should pay for their share," the budget blueprint states.

Trump Budget: FDA-Regulated Firms Should Pay 'Their Share' In User Fees

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A budget "blueprint" from the Trump administration asks for a major increase in user fees collected from medical-product companies in FY 2018 compared to what firms have agreed to. Meanwhile, the proposal appears to seek a significant reduction in funds provided by Congress to the agency for pre-market reviews, but details are lacking.

As is, the proposal could be a source of complication as the industry pushes for speedy reauthorization of the device user-fee program based on an agreement inked with the Obama administration's FDA last summer. But industry groups are being cautious in their response until they see more details.

The Trump administration issued its FY 2018 "budget blueprint" request March 16, slashing domestic spending while proposing big increases for defense spending and border protections.

The outline does not specify a budget total for FDA, but the US Department of Health and Human Services, as a whole, would be targeted with a 17.9% reduction. And the details that are provided for FDA in the blueprint are telling.

INDUSTRY WANTS MORE DETAILS

The plan "recalibrates Food and Drug Administration (FDA) medical product user fees to over $2bn in 2018, approximately $1bn over the 2017 annualized CR [continuing resolution] level, and replaces the need for new budget authority to cover pre-market review costs," the blueprint states.

"In a constrained budget environment, industries that benefit from FDA's approval can and should pay for their share," the White House Office of Management and Budget writes.

AdvaMed President and CEO Scott Whitaker told *Medtech Insight* that his group needs to see more details on the administration's preliminary budget proposal for FDA. But, he says, the group "remains committed to the medical device user-fee agreement as negotiated, which represents a substantial increase over current fee levels and will help speed new medical technologies to patients in need."

Whitaker added: "The medical technology industry has long recognized the benefits of a well-resourced FDA and would be concerned if the agency were to face significant budget cuts that would negatively impact the approval process."

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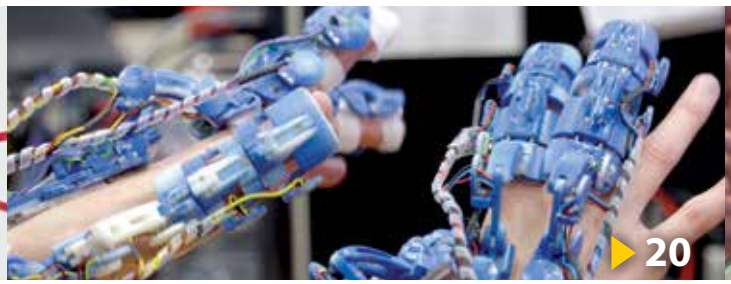

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India's Stent Price Slash Creating Climate Of Fear, Foreign Device-Makers Say

PENELOPE MACRAE

The Medical Technology Association of India (MTaI), made up of multinationals with significant investments in the country, says the government of Prime Minister Narendra Modi has gone the wrong route in slashing prices of cardiac stents by more than 75% and interfering in the dynamics of the market.

The National Pharmaceutical Pricing Authority (NPPA) last month slapped price caps on stents to end what it called "exploitative pricing." It said it wanted to make the devices more affordable for patients in a country where medical costs push tens of millions of people into poverty each year.

But MTaI said late last week the industry "has been broadly misunderstood" and declared device-makers "were mistakenly being looked upon as profiteering agents, forgetting the value they bring to the country."

MTaI was set up last year and founding members include **Johnson & Johnson**, **Bausch & Lomb Inc.**, **Smith & Nephew PLC**, **Boston Scientific Corp.** and **GE Healthcare**.

MTaI also said the pricing order failed to differentiate between stents based on their specifications. "The control of stent prices in the manner it has been done, with a shocking reduction of prices, may unfavorably skew the market for the patient and will affect adversely the business environment," the association said.

"While MTaI has been a believer of fair practices, the slew of measures has created an atmosphere of fear among the member companies," the association added. "The government must not undercut market dynamics."

The NPPA reported finding "unethical markups" at each stage in the supply chain, and a health ministry study showed stents were being sold at margins ranging from 270% to around 1,000%.

India, with its population of 1.25 billion people, and other emerging markets loom large for international medical device firms. Although developed markets still account for most sales, emerging markets offer faster expansion potential.

India's per capita medical device spend is a mere $3 compared with $7 in China, $21 in Brazil, $42 in Russia and $340 in the US, and its $3.7bn industry represents just 1.3% of the US-dominated global devices market of $335bn.

Bolstering this bullish outlook is that more Indians are joining the middle class and aging.

PRICE CONTROLS A VOTE WINNER?

But while India's government was vocally pro-business in its first two years in office, it's now sounding a more populist tone as it courts the still overwhelmingly poor electorate.

Prime Minister Narendra Modi, whose Bharatiya Janata Party racked up a landslide win March 11 in a crucial election in India's most populous state Uttar Pradesh, trumpeted on the campaign trail the decision to cap stent prices as proof of its government's commitment to create "affordable health care for all."

"When a person is suffering from a heart problem, a stent has to be put, but this stent was expensive and the poor could not afford it. We have ensured stents are affordably priced," Modi told one rally. He also noted that the government, since its election in 2014, had reduced prices of hundreds of drugs for diabetes, cancer and other diseases.

Still, despite Modi's talk about creating greater medical access, critics note that India's health outlay badly lags many other nations. The government, in its annual budget in February, hiked health spending by almost 28%, but the outlay as a percentage of GDP remained virtually flat at around 1% – far below a world average of close to 6%, according to World Bank data.

"The spending increase in the budget was welcome, but much more needs to be done," MTaI Director General Pavan Chaudary told a Mar. 10 news conference. He argued that rather than looking to price controls, the government should invest more in public health to ensure health-care coverage for all citizens. The association said: "In a clear absence of an adequate and equitable reimbursement structure, there is a mismatch in the policy framework."

The Uttar Pradesh victory will give Modi's party much more power in the national parliament, and business leaders hope the government may pursue market reforms more aggressively. But with national elections looming in 2019, many observers suggest the government's accent will be more on populist measures.

On Mar. 12, the NPPA cut prices of 54 cancer, hypertension, diabetes and other "essential" drugs by as much 55% as part of a government drive to make treatment of critical illnesses more affordable by lowering the costs of medicines. Drugs account for at least three-quarters of out-of-pocket expenditure, and some 61% of health-care expenditures is out-of-pocket in India, one of the world's highest rates.

MORE DEVICE PRICE CAPS?

The pricing regulator chairman Bhupinder Singh said the government is "working in the direction of bringing other medical devices under price control," such as pacemakers, orthopedic implants, consumables such as catheters, and intraocular lenses.

India's Alliance of Doctors for Ethical Healthcare has appealed in a letter to Modi "to put a cap on the prices of drugs, particularly generic and cancer medicines, and on intraocular lenses and knee and hip replacement implants, as those are also being charged exorbitantly like coronary stents."

MTaI said its members are committed to supplying the stent market at the new capped prices and denied media reports that manufacturers were withdrawing products and creating stent shortages. But the association suggested the move could discour-

age companies to innovate and bring in new technologies to India.

"If companies do not have the resources to invest in research and innovation, it is ultimately the public and the long-term health of the nation that will suffer," MTaI said.

The price caps reduced the cost of a bare metal stent to INR7,623 ($109) from an average price of INR45,000 and lowered the cost of a drug-eluting stent, which makes up more than 90% of the market, to INR29,600 from an average rate of INR121,000, a government statement said.

India brought stents under its price control regime last year but only announced the new prices following consultations with the industry.

Also, the association said, "the global investments into India that the government has been keen on, would not be possible without taking into consideration points raised by globally reputed and respected companies."

"This move could limit the accessibility of cutting-edge technologies in coronary stents for Indian patients, affecting both treatment quality and risking the high-growth medical tourism sector," said Himanshu Baid, medical technology division chairman at the Confederation of Indian Industry, an important business lobby group.

Critics of this point of view say, however, that the size of India's population size and rampant coronary disease make the country's market far too big for device-makers to restrict introduction of new devices – even if prices are capped – and that what the industry loses in pricing power it could make up in volumes. Heart disease is the country's top killer.

RISING PROTECTIONISM?

Medical device-makers are also contending with a more protectionist mood in the government, which has launched a flagship "Make in India" program in an attempt to create more jobs for the millions of Indians who join the workforce each year.

Most multinational medical device-makers have exported their products to India with the Indian government's inverted tariff structure, which has made imported finished goods often cheaper than imported raw materials, favoring such a model. India currently imports at least 70% of its medical devices from breathing and imaging equipment, pacemakers to robotics.

Last year, though, the government hiked import duties on medical devices by 7.3%, taking effective rates to as high as 28%, to boost domestic production, and Health Minister JP Nadda said in a statement that the price ceilings on stents will "promote 'Make in India' in a big way."

"Seeing the huge number of patients and future requirements, foreign companies will also try to make in India for cutting costs and remain competitive," Nadda added.

The association, though, cautioned that policymakers need "to realize the importance of global participation in the growth of Indian medical technology industry. Medical technology innovation can never be always completely indigenous.

Medical technology innovation "transcends the boundaries, and for its free flow across the globe, any protectionism would not be a facilitator, but will only sow seeds of doubt in the minds of global investors," MTaI added.

The group warned that pushing make in India without global help "is likely to overcrowd the lower end of the technology spectrum with manufacturing companies. This can congest that space and make native as well as global companies which are succeeding currently, fail."

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Could The City Hospitals Project Be A Bit Of A Turkey?

AHMET SEVINDIK

Siemens Healthineers' contract win last month to oversee the clinical lab service operations for two new hospitals in Turkey highlight just one of many more deals of this type that are expected to come as the country forges ahead with its City Hospitals project, which will see 29 giant, medical facilities constructed and added to the Turkish health care infrastrure by 2018.

Additionally, Siemens' other imaging rivals have also been busy carving out themselves a slice of this growing pie. In May last year, General Electric Healthcare (GE) signed a $95m deal with DiA Holding to supply 3,000 units of medical equipment – including magnetic resonance imaging, computerized tomography and life support machines – to Bilkent and Mersin hospitals. Toshiba has also signed a deal with Akfen, the company contracted to build Isparta City Hospital (755 beds), to provide medical imaging equipment including CAT scanners.

However, these multinationals may have the advantage over smaller players in trying to win tenders from the hospital construction companies. And there are also persistent problems that plague the Turkish health care market which put a tarnish on this potential growth opportunity.

BEWARE OF BIG BOYS

Both GE Healthcare and Siemens Healthineers had conducted tough negotiations with DiA (now acquired by CCN) and Toshiba with Akfen before winning their respective contracts. In the high–tech end of the medical equipment market, big players like GE, Siemens, Toshiba have the advantage of already being active in Turkey's private health care market and knowing the lay of the land there. However, the slowing down of investments in new private hospitals over the last two to three years, as well as the debt crisis of university hospitals (see below) means the new city hospitals offer a more attractive market for these multinationals and they are looking to capitalize on this opportunity aggressively.

Mid-sized companies from other parts of the world, with sound and competitive products, could look to profit from the City Hospitals project and move into the Turkish market for the first time. But before doing so, these companies would need to go through the Ministry of Health to gain regulatory approval for their products. Only after these products are registered in the Product Monitoring System of Turkey and given a price by the Ministry, then are they able to take part in these tenders. They do not have to establish a base in Turkey; instead, they could find a distribution partner for their products. International fairs and trade chambers are good platforms to establish and foster new business relationships. In the low–tech, disposable products end of the market, competition to win tenders for the city hospitals is intense, though it is mostly between local companies.

PAYMENT PAINS STILL TO EASE

Although the City Hospitals project widens significantly the playing field in Turkey, the country's health care sector still faces problems that make life difficult for many big, medium and small companies. Turkey's university hospitals are still deep in debt, owing suppliers of medical devices and services as much as TRY 4bn ($1.1bn). *(Also see "Turkish Hospitals' Billion-Dollar Debt A Top Priority For Medtech Suppliers" - Medtech Insight, 12 Jan, 2017.)*. Currently, it could take as long as four years for suppliers to get paid by these hospitals. While the Turkish government and medtech industry struck a deal at the end of 2016 to have the Ministry of Finance pay this debt, the agreement still needs to be rubberstamped by Parliament and nothing has happened so far. To make matters worse, Ministry hospitals have started also to set 5–6 month terms for paying suppliers.

Reimbursement from Turkey's public payor, Social Security Institution (SGK), to companies have also added to the delay in payment. Moreover, reimbursement prices have not changed since 2007 and this is a significant problem particularly for low- and medium-tech products and consumables, such as stents, prostheses, surgical threads, syringes, among other things.

While the Turkish government has made known that it wants to expand local production of medical instruments, just as it does for medicines as well, industry analysts believe that this would be very difficult to achieve, without these payment problems being resolved first.

THE COMPANIES BEHIND TURKEY'S CITY HOSPITALS

These hospitals are being built by private companies, like DiA Holding. Private companies will be operating new hospitals for the next 25 years. They will be operating many services in the hospital including medical imaging, laboratories, IT, security, catering and car park. Government will be providing medical staff. The Government will be paying rent to private companies, who built the hospitals, for 25 years. The companies will be able to run commercial enterprises at hospitals' near surroundings like shops or restaurants. In order to make the deal sweeter the Government guarantees a minimum number of patients for these hospitals every year. In most of them 70 % capacity use is guaranteed. If the number of patients stays under this level, then the Government will pay compensation for missing patients and dropping revenue.

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Last August, the device industry reached a user-fee agreement with FDA calling for $1bn in fees, plus inflation, spread over five years to support medtech product reviews and improved performance goals, including "total-time-to-decision" goals for PMAs and 510(k)s, and new targets for *de novo* reviews and pre-submissions. *(Also see "Industry, US FDA Strike $1Bn Deal After Contentious User-Fee Negotiations" - Medtech Insight, 23 Aug, 2016.)*

As part of the August 2016 agreement – covering FYs 2018-2022 – the agency also promised to review its processes and investments in software oversight, real-world evidence and patient engagement. *(Also see "MDUFA IV Takes Shape: A Catalogue Of Draft Commitments" - Medtech Insight, 29 Aug, 2016.)*

The Alliance for a Stronger FDA – a group that has always pushed for higher funding levels for the agency – was also critical of the budget blueprint.

"The president's proposal funding mechanism – cutting more than a third of the agency's appropriation and offsetting it with an enormous increase in medical product industry user fees – is neither wise nor realistic. Not wise, because FDA's core responsibilities, safe and effective medical products, and safe foods, need to be supported in large measure by the public, who is the primary beneficiary," the group stated.

The alliance added that the president's proposal was not realistic because "the device and drug industries have recently completed user fee agreement negotiations with FDA, concurring upon an appropriate amount of industry fees to support agency.

INDUSTRY AGREEMENTS IGNORED?

About $1.4bn in user fees is supposed to be collected by FDA in FY 2017 from the medical device, pharmaceutical, generic drug and biosimilar user-fee programs. According to the reauthorization agreements reached last summer between industry groups and FDA, the agency is supposed to collect about $1.7bn in fees from the four program next fiscal year.

A plan to collect "over $2 billion" in fees suggests a demand by the administration to go beyond the user-fee agreements, which have yet to be approved by Congress. And the proposal to "replace" congressionally appropriated budget authority for pre-market costs may run counter to a standard element of the user-fee agreements – a minimum appropriations amount that is necessary to "trigger" user-fee collection. The appropriations trigger established in the MDUFA IV reauthorization agreement is about $320.8m, according to MDUFA IV documents, "to provide assurance that user fees will be additive to Budget Authority appropriations."

The device industry is pressing for Congress to address the MDUFA IV user-fee reauthorization, according to the agreement inked with FDA during the previous administration. The current, MDUFA III program is set to expire Sept. 30 and, if a reauthorization plan is not approved by mid-summer, it is expected that layoff notices will need to be sent to user-fee-supported FDA employees.

No hearings have been held yet on the device agreement. But the Senate Health, Education, Labor and Pensions (HELP) Committee has scheduled a session to address reauthorization of all of FDA's user-fee programs, including devices, for March 21.

The budget blueprint also states: "To complement the increase in medical product user fees, the budget includes a package of administrative actions designed to achieve regulatory efficiency, and speed the development of safe and effective medical products." But no details have been included yet.

'CONGRESS HAS POWER OF THE PURSE,' HOUSE APPROPRIATOR TELLS WHITE HOUSE

Health-policy experts point out that a president's budget is typically the beginning of a negotiation and does not reflect the policies that will actually be enacted.

The budget blueprint from the White House "is just one part of the process, not the final determination," Mark McClellan, who directs the Robert J Margolis Center for Health Policy at Duke University, told *Medtech Insight*. McClellan previously ran FDA and the US Centers for Medicare and Medicaid Services. He added that Congress has a long history of supporting user fees and that user fees are intended to supplement, not replace, FDA appropriations.

"As directed under the Constitution, Congress has the power of the purse," House Appropriations Committee Chairman Rodney Frelinghuysen, R-NJ, said in response to the White House's request. "While the president may offer proposals, Congress must review both [budget and supplemental] requests to assure the wise investment of taxpayer dollars," Frelinghuysen added.

Sen. Lamar Alexander, R-Tenn., who chairs the Senate HELP Committee, concurred. "The president has suggested a budget, but under the Constitution, Congress passes appropriations bills," he stated.

A DEEP SLICE INTO NIH BUDGET

Sen. Alexander was also critical of a proposed 22% cut to the National Institutes of Health's budget, which would reduce funding to $25.9bn.

Alexander remarked: "As a member of the Senate Appropriations Committee, my priorities are national defense, national laboratories, the National Institutes of Health and national parks. We will not balance the budget by cutting discretionary spending, which is only 31% of spending and is already under control because of earlier budget cuts."

On the Democratic side, House Energy and Commerce Committee Ranking Member Frank Pallone, D-NJ, was also alarmed by Trump's budget blueprint. "The budget proposal could ... endanger our nation's pipeline of innovative drugs and medical devices by endangering funding for FDA. … This proposal could threaten the agency's ability to hire and train medical product staff, carry out critical activities to ensure safety and effectiveness of our [medical products] … and is not a serious proposal."

Ferdous Al-Faruque and Derrick Gingery contributed to this report.

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CMS Administrator Seema Verma: What Industry Can Expect

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Seema Verma's March 14 swearing-in as administrator of the US Centers for Medicare and Medicaid Services makes the former health-policy consultant and head of Indiana's Medicaid "HIP" (Healthy Indiana Plan) program a key player in implementing the Trump administration's vision of health care.

The vote in the US Senate to approve Verma to run CMS – which handles $1tn worth of Medicare, Medicaid and CHIP (Children's Health Insurance Program) payments, annually – fell mainly along party lines, with Republicans supporting her and Democrats opposed. Her written answers to detailed questions from lawmakers, mostly Senate Democrats, during her confirmation process provide some insights into which programs at the agency she might support, and other regulations and projects she might limit or suspend.

Now that she has taken on the mantle at CMS, Verma likely will ask for more input on the way outcomes from accountable care organizations, which are groups of hospitals, doctors and other providers that work together meeting cost and quality metrics are measured, and may scale back regulations affecting ACOs. She may also investigate if the Protecting Access to Medicare Act of 2014 (PAMA) rules on appropriate-use criteria are limiting patient access to advanced imaging; and is expected to limit, or make voluntary, several ongoing payment or delivery programs launched by the Center for Medicare and Medicaid Innovation (CMMI), a group created by the Affordable Care Act (ACA) to try out and launch models to promote value-based health care.

Like her boss, HHS Secretary Tom Price, Verma favors repeal and replacement of the ACA, she is opposed to Medicaid expansion and she wants to give low-income beneficiaries state-run, consumer-directed health savings accounts to purchase the type of insurance coverage they want, as a substitute to ACA's guaranteed coverage of up to 90% of a Medicaid recipient's health-care costs.

> "Patients and their doctors should be making decisions about their health care, not the federal government," Verma said at her confirmation hearing last month.

"Patients and their doctors should be making decisions about their health care, not the federal government. We need to ensure that people have choices about their care," Verma testified at her mid-February confirmation hearing before the Senate Finance Committee.

"CMS' rules and regulations shouldn't drive doctors and providers away or crowd out care, but should instead support them in delivering high quality care to their patients," she added.

Whether the House-Republican American Health Care Act (AHCA) "repeal and replace" plan is ultimately approved by Congress remains to be seen. In the Senate, in particular, the bill is opposed by Democrats and a mix of moderate and far-right Republicans. But Price and Verma are expected to move ahead as if the ACA will shortly be replaced by the AHCA, and take what actions they can to deregulate ACA-inspired CMS programs.

Below is a roundup of Verma's statements and positions in five policy areas the impact the device sector.

RURAL PROVIDERS "NOT READY" TO TAKE ON ACO RISKS

Verma responded to Sen. Maria Cantwell's, D-Wash., questions about the effectiveness of ACOs – payment models that emphasize value-based care. Verma said the traditional fee-for-service system under Medicare "can encourage unnecessary spending by putting too many health-care decisions in the hands of a distant federal bureaucracy rather than in the hands of doctors and their patients." She also said "all health-care providers, from primary care providers to specialists, should be encouraged to provide value to their patients."

But whether the new CMS chief embraces further development of ACOs is likely to depend on if health-care providers in rural states and industry stakeholders agree that ACOs have been successful, and that they had enough input into the way the alternative payment models are set up. She told Sen. Ron Wyden, D-Ore., on Feb. 16 that many rural providers "aren't ready to take on the risks" that ACOs entail. *(Also see "CMS Nominee Seema Verma Urges Caution On Competitive Bidding Program" - Medtech Insight, 17 Feb, 2017.)*

Verma's cautious approach to supporting alternative payment models (APMs) dovetails with AdvaMed's warning to CMS in June 2016 comments on APMs and ACOs that "adjustments for certain new technologies are necessary" under some ACO and bundled-payment programs to "ensure certain Medicare beneficiaries have access to a full range of treatment options." Industry groups might expect a sympathetic ear from Verma on challenges companies face in getting fair reimbursements under the alternative, value-based models.

VERMA CITES "BURDENS" IN ADVANCED IMAGING CRITERIA

Under PAMA, and under the Medicare Access and CHIP Reauthorization Act (MACRA), providers are subject to physician quality reporting system (PQRS) cardiology measures. As part of this, ordering physicians are encouraged to consult appropriate-use criteria before referring Medicare patients for advanced diagnostic imaging. For example, three of the physician quality measurements for cardiologists set by CMS in consultation with specialty groups in 2016 are designed to get cardiologists to consult appropriate-use criteria for cardiac stress procedures in low-risk surgeries before ordering them. *(Also see "CMS Current Quality-Pay Programs Unlikely To Reward Device Innovations" - Medtech Insight, 12 May, 2016.)*

Also, under PAMA, providers are asked to rely upon evidence-based appropriate-use criteria for advanced imaging studies starting this year, and will not be reimbursed by Medicare for advanced imaging after Jan. 1, 2018, unless they can document which criteria was consulted, according to the American College of Radiology (ACR). CMS has already approved the ACR as a supplier of clinical-decision support software to help clinicians make the most appropriate treatment decision for each patient's specific condition.

But Verma told Sens. Debbie Stabenow, D-Mich. and Michael Bennet, D-Colo., that she wishes to "closely monitor challenges" associated with implementation of the PAMA rules on appropriate-use criteria. She said will be "identifying and evaluating specific burdens that have the potential to limit patient access" to advanced imaging.

SCALING BACK CMMI PROJECTS

After and during her confirmation hearings, Verma took questions from at least five Senators (Wyden, Cantwell, Sherrod Brown, D-Ohio, Mark Warner, D-Va., and Ben Cardin, D-Md.) about whether she would advance, suspend or cut back on CMS's CMMI demonstration and payment programs to promote value-based care.

She seemed familiar with the innovation center's various approaches to lowering health care costs and improving quality for Medicare and Medicaid beneficiaries, and talked in favorable terms about at least one of the programs, for hospice care.

HHS Secretary Price is on record, as a congressman, forcefully opposing mandatory programs developed by CMMI as a congressman, and Verma is not expected to differ in that position. *(Also see "Fierce Critic Of Obamacare, Medicare Delivery Reforms Tapped To Run HHS" - Medtech Insight, 29 Nov, 2016.)*

The administration's sentiments about some of the CMMI payment models was put on display in a notice issued March 20 delaying the start-date for the Comprehensive Care for Joint Replacement (CJR) *(Also see "Total Joints: Bundled Payments Driving Procedural Innovation" - Medtech Insight, 26 Apr, 2016.)* and a cardiac bundled payment models *(Also see "Cardiac Care Bundled Pay Models Preserve New Tech Add-Ons, But Still Make Medtech Nervous" - Medtech Insight, 5 Jan, 2017.)* until October to give more time to collect public feedback.

LABORATORY PAYMENTS

An update to the way Medicare reimburses lab tests was approved as part of the 2014 PAMA law, and finalized into a regulation by CMS in June 2016. *(Also see "Labs Get Extra Year To Adjust To Diagnostics Reimbursement Revamp" - Medtech Insight, 20 Jun, 2016.)* The reforms require labs to report to CMS their private-payer payment rates and test volumes, and the agency will base Medicare reimbursement on those market rates. Both AdvaMed and the American Clinical Laboratory Association applauded the market-based provisions when they were initially passed in April 2014. *(Also see "Medicare Dx Payment System Will Be Market-Based, More Transparent Under New Law" - Medtech Insight, 3 Apr, 2014.)*

However, since then, some regional and community-based labs have been complaining to their Senators about whether the data correctly reflects all laboratories' reimbursement information, saying the exclusion of market data from hospital outreach labs will impact the accuracy of CMS' data.

Verma told lawmakers, "We should certainly strive for accuracy in this market data collection process," and that, as administrator, she would try to meet with regional and community-based laboratories "to discuss workable solutions." She also acknowledged to Sen. Bill Nelson, R-Fla., that she sees "challenges" with the data-collection process, and she is concerned that burdens with the data collections might limit patient access.

The CMS administrator could revisit or change the way data is collected from hospital outreach labs, after she reviews the data collection process.

ENTHUSIASTIC TELEHEALTH SUPPORT

Verma told Sen. Mark Warner she shares his interest in promoting telehealth, saying it "can provide innovative means of making health care more flexible and patient-centric."

She said that she intends to try to expand telehealth access within rural and underserved areas, and believes it may be "one of the best means to offer patients increased access, greater control and more choices to fit their medical needs.

Providers and telehealth equipment makers can expect Verma to push for expanded reimbursements for telehealth. Sens. Johnny Isakson, R-Ga., Warner, Wyden, and Orrin Hatch, R-Utah sponsored provisions last year under the Chronic Care Act that would allow expansion of payments for telehealth services, and they are likely to push the matter again this year. *(Also see "Chronic-Care Bill Would Extend Pilot On Use Of Home-Care Devices, Promote Telehealth" - Medtech Insight, 28 Dec, 2016.)*

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Classified: Next-Gen Sequencing Analyzers, Mobile Glucose Monitoring, Restless-Leg Devices

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Three significant *de novo* classifications from the past several years were made official this week by US FDA. The agency issued orders designating high-throughput next-generation sequencing analyzers, "secondary displays" for continuous glucose meters, and vibratory counter-stimulation devices into class II with special controls.

FDA handed down the positive *de novo* decisions in 2013 and 2015, but the March 14 orders formally record the new class II device types and the marketing standards for future devices in the same categories. FDA is also moving toward exempting future devices of these types from having to submit a 510(k).

Each of these device categories is included in FDA's March 14 listing of products proposed for 510(k) exemption.

MOBILE GLUCOSE MONITORING

In the first order, the agency addresses secondary displays to continuous glucose monitors (CGM). Formation of this class II device category (21 CFR 862.1350) was the basis of a 2015 marketing go-ahead for an update to **Dexcom Inc.**'s *G4 Platinum Continuous Glucose Monitoring* System, specifically to allow the system to transmit data to an *Apple* mobile device wirelessly via the *Dexcom Share Direct Secondary Display*. The secondary display refers to mobile devices, such as a smartphone or smartwatch app, that can be used by a caregiver to remotely monitor glucose levels detected by the primary CGM device. It's not something that measures glucose levels directly.

Dexcom says the class II designation was important to future mobile-app development for CGMs. The notice provides a 60-day comment period, and then, according to a provision in the 21st Century Cures Act, enacted in December, FDA has an additional 60-days to issue a final list of exempted devices.

FDA says the secondary display device type is prone to three specific risks: reporting of incorrect glucose value or the value being missed due to a cybersecurity breach; treatment recommendations being made based on data from the secondary display device instead of the primary device; and the chances of patients becoming overly reliant on others to monitor their glucose levels using the secondary display.

To avoid these risks, the agency is requiring three special controls:

- Protecting the secondary monitor from unauthorized access to data and modification of data;
- Labeling must clearly state that dosing decisions should not be based on the secondary display; and
- Labeling must state that the secondary display is not intended to replace physician-advised self-monitoring practices.

NEXT-GEN SEQUENCING MILESTONE

The next order relates to a seminal FDA *de novo* clearance from 2013, the first marketing go-ahead by the agency of a next-generation sequencing (NGS) analyzer platform. *(Also see "FDA Approves First Next-Generation DNA Sequencing Platforms" - Medtech Insight, 20 Nov, 2013.)*

The March 14 order formally establishes a class II category (21 CFR 862.2265) with special controls for "high-throughput genomic sequence analyzer[s] for clinical use." In this case, the order states that FDA is "planning to exempt the device from pre-market notification requirements." The NGS analyzer category is also included on FDA's March 14 proposed 510(k)-exemption list.

Even without a 510(k), the analyzers still need to meet labeling requirements.

The order comes out of Illumina's *de novo* classificationrequest for its *MiSeqDx Platform* NGS instrument, which was cleared for marketing in November 2013. In parallel to the 2013 decision, FDA granted *de novo* and class I status for the *Universal Kit 1.0* for labs to develop sequencing assays, and 510(k) clearances to the first assays for the *MiSeqDx* instrument, for cystic fibrosis. Since then, FDA has taken steps to develop a coherent regulatory framework for NGS that puts heavy emphasis on use of accepted standards and shared databases. *(Also see "US FDA's Next-Gen Sequencing Guidances: One Stop On A Pathway" - Medtech Insight, 26 Jul, 2016.)*

In the new order, FDA says the NGS analyzers are prone to inaccurate results if necessary components of the instrument systems are missing and when the performance of the system is unknown. To overcome these risks, the agency is asking makers of the devices to meet several labeling special-control requirements.

"The special controls for a high-throughput genomic sequence analyzer for clinical use include a detailed outline of analytical performance information that must be generated for the instrument system (i.e., platform and all associated software)," says FDA. "This includes analytical validation using well characterized samples (i.e., well characterized or reference materials) to demonstrate the system's capabilities and to identify limitations."

The agency notes that validation testing required through special controls only

establishes the instrument's general capabilities, but doesn't establish its ability to meet diagnostic claims. Instruments that make specific diagnostic claims, including those that make claims for a specific test, such as an oncology panel, do not fit in "high-throughput genomic sequence analyzer" category and will require additional independent validation, according to FDA.

RESTLESS-LEG DEVICE

Finally, FDA issued an order establishing a class II device category (21 CFR 882.5895) for vibratory counter-stimulation devices, used to improve sleep in patients with restless leg syndrome (RLS).

Sensory Medical Inc. asked FDA to classify its *Symphony* device used to help patients with RLS sleep in 2011, leading to a *de novo* classification in 2013. *(Also see "Regulatory Briefs: Consensus Standards; Penalty Amounts Increase; Biologics Center Seeks Branch Chief" - Medtech Insight, 3 Feb, 2014.)*

The device category describes a system that produces electrically powered mechanical vibration to improve the quality of sleep in patients with RLS.

The agency identified risks including pain, discomfort, worsening of RLS symptoms, electrical shock, burns, adverse skin reactions and interference with other medical devices.

According to the order, 510(k)s must be submitted for this device category in the future. However, the vibratory counter-stimulation class is also included in the March 14 notice of proposed 510(k)-exempted devices.

Special controls for this device-type include:

- Appropriate analysis and testing to demonstrate electromagnetic compatibility (EMC), electrical safety, and thermal safety;
- Proper validation of the device firmware or software;
- Biocompatibility testing;
- Non-clinical testing; and
- Labeling requirements.

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With ENVI's 'Yes' Vote, EU Regs Could Come Into Force As Early As Mid-May

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The European Parliament's Committee for the Environment, Public Health and Food Safety (ENVI) voted in favor of the latest texts of the Medical Devices Regulation (MDR) and the IVD Regulation (IVDR) on March 21, recommending the new rules be adopted by Parliament.

The documents, which have already been adopted by the Council of the EU, now go forward to the plenary session of the European Parliament for a vote and possible adoption in early April (around April 4 or 5).

This means that progress is on track and that the texts are likely to be published in the *Official Journal of the EU* at the end of April or beginning of May. The latest timetable is:

WHAT	WHEN
New MDR and IVD to first enter into force within the European Economic Area	20 days after publication in *Official Journal of the EU*: between mid-May and early June.
Regulations to be fully applicable in EEA	Three years after entry into force for the MDR and five years after entry into force for the IVDR.

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IVDs Should Get Equal Focus To Devices In EU Reg Implementation, Industry Says

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The EU medtech industry says the European Commission and the EU competent authorities must ensure a balanced approach between the Medical Device and IVD Regulations when it comes to implementing the new frameworks.

John Brennan, director of regulations and industrial policy at industry group MedTech Europe, made the point at a March 9 meeting in Brussels organized by the European Commission and competent authorities. Brennan has recently taken over responsibility for IVD regulatory matters from Jesus Rueda, who is now focusing on international regulatory issues full time.

In his expanded role, Brennan emphasized the issue of balancing medical device and *in vitro* diagnostic interests in Brussels. He told meeting attendees that there is currently a danger of an imbalance forming in the proposed work programs for medical devices and IVDs.

A glance at the clusters program identifies priorities for implication by policymakers, indicating a heavy focus on medical devices at the moment. While there is a specific IVD cluster, the focus is different, Brennan commented. The IVD cluster – one of seven – is written at a strategic level, he told *Medtech Insight* in a recent interview, whereas the device parts are written at a more detailed, technical level.

MedTech Europe wants both industries to be addressed equally, either staying technical or strategic on both, Brennan emphasized at the stakeholders meeting, which was focused on the practical aspects of implementation of the EU Medical Devices (MDR) and IVD Regulations (IVDR).

RESOURCE AND TIMING CONCERNS

Industry is concerned the authorities may not recognize the resources, time and investment that is needed to make certain features of the IVD Regulation work.

While capacity demands will impact implementation of Medical Devices Regulation as well, there are particular concerns about notified body availability and capacity for auditing IVDs. There could be a huge bottleneck given that 85% of the IVD industry will be needing the services of a notified body for the first time.

> "There are very specific areas where the approach differs significantly between medical devices and IVDs – for instance, clinical data, where you would need separate work," MedTech Europe's John Brennan says.

Other critical aspects that need to be adequately addressed include classification, clinical evidence and conformity assessment, Brennan said. In particular, he wants these matters to be addressed by the European Commission's IVD technical group, which was due to meet this month.

Brennan said MedTech Europe is not calling for an approach where there are shadow meetings doing the same work for medical devices and for IVDs.

"Our point is that there are many areas where there is common work - such as UDI [Unique Device Identifiers], for example. But then there are very specific areas where the approach differs significantly between medical devices and IVDs – for instance, clinical data, where you would need separate work," he said.

"We are not asking for lots more clusters," Brennan said. "But, rather, within the IVD cluster we want to make sure we take care of everything, and devote the appropriate resources and timings to make sure it gets done."

Almost all IVDs must be newly classified under the new IVD Regulation, so challenges are expected.

Even if the classification rules are well written and generally clear, the intended purpose of a product can change the risk classification of a product from a B to a C, for example, and hence alter the conformity assessment and clinical requirements that must be met. It will be useful to have guidance to address gray areas, Brennan said.

Indeed, it seems guidance is likely to be forthcoming. The European Commission has indicated its interest in getting the results of an exercise MedTech Europe performed exploring the challenges presented by products on the borderline between two classes. The trade association hopes this effort might form the beginning of a European Commission IVD classification guidance document.

CLINICAL EVIDENCE

Clinical evidence is also going to be needed for the first time for the majority of IVDs. And there are questions over what type of data is needed for legacy products, i.e., those products already on the market, including devices linked to safe clinical use for decades, Brennan explained.

Manufacturers need to understand the expectations for such products, in terms of accuracy and scientific evidence, for example, and how that information should be compiled and presented. Companies will need information soon on what forms and templates to use so that they do not waste resources trying to address the new requirements in the wrong way, Brennan said.

The information is crucial, he said, because companies need to decide whether to update, retire or replace their products, Brennan said. Similar questions exist for legacy medical devices.

MORE QUESTIONS THAT NEED ANSWERING

When it comes to performance evaluation for IVDs, templates for performance evaluation reports and post-market follow up are sorely needed. Other questions that are circulating to support implementation of the IVDR:

- What does "generic device group" mean?
- What does the phrase "category" mean for IVDs with respect to conformity assessment?
- And, how does the industry migrate from the list-based Common Technical Specifications, as they are known under the Medical Device Directives, to the risk-based Common Specifications for class D IVDs under the IVDR?

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UK Guidance On Leadless Pacemakers Is A Prelude To Requirements Under EU MDR

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The UK Medicines and Healthcare products Regulatory Agency has issued guidance on the pre- and post-market clinical evaluation of leadless cardiac pacemakers, a type of technology that the regulator says is not yet well-established and for which no specific product standards exist.

European CE markings for leadless pacemakers have to date been issued on the basis of limited clinical data, in terms of both the number of patients included in clinical studies and the duration of their follow-up, according to the MHRA.

The agency says it wants to see more clinical guidance on the use of leadless pacemakers combined with robust surveillance of safety to ensure that this new technology is used appropriately and that the risk of patient harm is as low as possible. Among other things, it recommends that all leadless pacemaker implants should be entered into a comprehensive registry or post-market clinical follow-up (PMCF) study, held and funded by the relevant manufacturers and maintained to the standards of good clinical practice.

The content of the MHRA guideline "is in line with the new expectations" regarding high-risk implants as outlined in the recently-published EU Medical Device Regulations, said Gert Bos, executive director and partner at consultancy firm, Qserve Group. *(Also see "EU Industry Says Real Work Starts Now On Regulations" - Medtech Insight, 23 Feb, 2017.)* "[The] good thing is that the guidance provides some ranges of patient sizes, minimum data points etc. So in a way it might be seen as a prelude to one of the hopefully many common specifications that will become part of the new system [under the MDR]," he told *Medtech Insight*.

Shutterstock: Have a nice day Photo

The EU MDR, when in force, will require much more PMCF data to be generated, Bos said, adding that only joining a registry might not be sufficient for manufacturers to demonstrate they have provided enough clinical data. "Registries have advantages such as covering all patients, and [also] disadvantages such as being non-specific to the device in question," Bos said. There are many more options available for collecting data, he said, noting that meeting the PMCF requirement is likely to be burdensome for manufacturers.

The MHRA guidance covers new leadless devices and all design changes or iterations and enhancements that might affect the product's clinical safety or performance. For each device modification, it recommends that sponsors should individually assess whether all aspects of the guideline apply. For example, it points out that appropriate follow-up duration may be needed for changes that impact only the ease of placement of the leadless device.

While the MHRA's guideline principally applies to leadless pacing, the agency envisages that it may also be applied to other leadless cardiac implantable electronic devices. The agency intends to revise the guideline periodically as the evidence base for these technologies grows.

The MHRA seems to have taken the lead with respect to developing guidance on leadless pacemakers, Bos noted. He commented that there has been some concern that high-risk implants in Europe have historically reached the market with insufficient clinical data, and that post-market clinical follow up of such products has typically been underdeveloped.

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Lack Of Monetization Know-How Hits Price Margins For Medtech

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Pricing pressures persist in the medtech industry, but the biggest challenge that companies are facing is how to fully monetize new products, services or solutions that they bring to the market. As a result, firms struggle to mitigate the effects of continuous price erosion on their existing product lines and profit growth stagnates.

These are the findings from Simon-Kucher & Partners' 2017 Medtech Barometer, an annual survey of the European medtech industry about expectations for the year ahead.

Medtech Insight had an exclusive preview of the survey responses prior to the official unveiling, which is planned for March 22 at SKP's 9th European Medical Technology Strategy Forum in Frankfurt, Germany. The responses came from 33 C-suite executives, functional heads and private equity investors operating in the EU medtech sector.

OUTLOOK POSITIVE

The overall outlook of the respondents was positive for 2017, with 55% expecting business to be better this year than 2016, 36% expecting it to be the same, and only 9% expecting it to be worse than last year. Increasing penetration in developing markets and rising investments in health care due to aging populations were cited as reasons for optimism, while pressure from low-price competition and increased procurement professionalization were central concerns that clouded the 2017 outlook.

What was surprising in this year's survey findings are just how dramatic the average price drop is expected to be for 2017, compared to previous years, according to Joerg Kruetten, head of SKP's global life sciences practice.

"For the medtech industry, which is so innovation-driven, price erosion in itself is nothing traumatic," Kruetten told *Medtech Insight*. "As products mature, it is expected that they cannot command the same price range as when they first came out. That's fine and companies can still operate at a decent margin, as long as they launch new products that achieve a price premium, which then stabilizes and balances out the price erosion."

In SKP's prior-year pricing surveys, respondents expected positive – albeit small – price increases, of 0.34% in 2015 and 0.35% in 2016. As Kruetten pointed out, this reflects the impact of product innovation launches to offset pricing pressures on legacy products. However, in the 2017 Medtech Barometer survey, respondents forecast that the tide will turn, expecting average prices to actually fall 0.32% in 2017.

"We were surprised to see the drastic change," said Kruetten. "It seems the price situation has got even worse; companies are not able to stabilize price to the extent that they have been able to in the past. Customers are forcing companies to lower the price on existing products, and they are not willing to pay the premium on the new product."

CHALLENGES OF MONETIZING

The key reason, it appears, is the lack of understanding among companies on how they can extract the most value from their innovations and then monetize the opportunity. Indeed, when respondents were asked to rate themselves on their competency in monetizing the potential of their new products, new services or new solutions, using a scale of one to five (one being not competent and five being very competent), the best score was a mediocre 3.06 for monetizing products. The median rating respondents gave themselves for monetizing new services was 2.52 and the median rating for monetizing new solutions was 2.45.

Kruetten explained why companies believed themselves to be best – relatively – at monetizing products, as opposed to monetizing new services or solutions. "The traditional medtech business model is very much product- and technology-centered. Many companies are more comfortable about determining a price for products than with services," he said.

"Services, traditionally in the medtech world, are provided free of charge, and that expectation of free service continues, while product prices are going down," Kruetten explained. "It is very difficult to start charging for services because customers are used to getting it for free and it is even harder to prove that providing services might lead to securing more traditional product business. Those are the key challenges in the context of service monetization.

"On the solutions side, that is a big trend right now, that companies go beyond offering pure devices, pure products. These solutions – for example, Medtronic is now offering to run cath labs as a solution for hospitals – require very comprehensive contracts. Selling these solutions and deploying them over a period of 3-4 years while making sure you are getting return on investment is a very complex and challenging undertaking."

To successfully monetize innovations goes far beyond plain product- and feature-selling. SKP has these tips to help companies realize more fully the potential of their new products, services and solutions:

1. Product monetization:
   a) Demonstrate and sell true added value
   b) Translate added value into incremental willingness-to-pay
2. Service monetization:
   a) Leverage services to differentiate and drive revenues
   b) Balance service investments with account profitability
3. Solution monetization:
   a) Drive customer lock-in and reduce "pure" price pressure through integrated and comprehensive solution offerings
   b) Access new value pools and generate incremental revenue through intelligent solutions beyond pure product.

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Latest Mako Tech Fleshes Out Stryker's Robotic Joint Replacement Line But Cost Critics Still There

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Uptake of **Stryker Corp.**'s recently launched *Mako* system for performing total knee replacements – the third approved application of the robotic arm – is expected to be quick due to the need for technology that can improve clinical outcomes in this procedure. However, the company would have to spend resources generating more clinical data to convince skeptics that the cost of a robotic-assisted system justifies the advantages such a technology could offer.

Stryker officially introduced the Mako total knee system to much fanfare on Mar. 16, at the Annual Meeting of the American Academy of Orthopedic Surgeons (AAOS 2017) in San Diego. The total knee application, for use in conjunction with Stryker's *Triathlon Knee*, had already won US FDA approval in 2015 but a widespread roll-out was intentionally delayed and it has only been used for this indication on a limited basis in 65 hospitals in the US, UK, Australia and Germany. However, the *Mako Robotic Systems* have already been widely used to perform partial knee and total hip replacements.

"This week is all about an educational piece for us, introducing the total knee application to the US market," William Huffnagle, president of Stryker's Joint Replacement division, told *Medtech Insight*. "When we look at what we like to accomplish here, this is really about surgeons, for the first time, getting to see the application. It's a disruptive technology, because it basically is allowing them (surgeons) to do things in a total knee procedure that they've never been able to do before."

Huffnagle told *Medtech Insight* that 20-30% of all total knee replacement patients are not satisfied with their knee implant, and added, that anecdotally, surgeons who have used the Mako total knee system, believe they can do a better job using this tool.

Wells Fargo senior analyst, Larry Biegelsen, wrote in a Mar. 16 research note that he expected the adoption of the Mako total knee replacement to be more akin to the quick adoption of Mako's partial knee system, rather than the slow adoption of its total hip replacement, due to a "perceived need for the improvement of outcomes of total knee replacement (like partial knees)."

"In our base and aggressive case scenarios, we expect the Mako total knee to represent 9% and 11%, respectively, of the US total knee market in 2021," he forecasts.

Stryker has placed more than 350 Mako systems in the US with more than 1,400 total knee procedures performed in four countries. (See Figure 1.)

THE MAKO EXPERIENCE EVENT

During Stryker's Mar. 16 launch event, dubbed "The Mako Experience", for the total knee system, Huffnagle moderated a panel discussion with three surgeons, who have been using the Mako system, to drive that message home to the more than 3,000 orthopedic surgeons attending the extravaganza.

While all three surgeons highlighted the benefits of using the Mako total knee system, they also acknowledged that there is a learning curve involved.

Panelist Kirby Hitt, an orthopedic surgeon in Temple, Texas, praised the precision, accuracy and safety of the Mako system, but said the biggest difference for him was in the improved balancing of the knee.

Matthew Abdel, an orthopedic surgeon at the Mayo Clinic at Rochester, Minnesota said the Mako robot has shown to be a great learning tool for residents and fellows at the teaching institution, and for himself.

Hitt said getting used to the robotic technology took a learning curve (of about 10 cases), but added it was quick and worth it to achieve better results.

Abdel agreed, "Any time you're learning a new technology, there is a learning curve … but the learning curve is quick … I would say that after about 5-10 cases that became almost neutral for us, and you can see it quickly come down on each case."

Martin Roche, an orthopedic surgeon, whose practice comprises 20 orthopedic surgeons in Fort Lauderdale, Florida, said since he started using the Mako system for partial knee replacements in 2006, the total joint procedure volume increased by roughly 20%.

"Even though patients who were coming in to look at the technology may not have been a candidate for that procedure, but they still wanted their total knee done," Roche told *Medtech Insight*. He said the hospital invested in another robot with five surgeons now using robotic technology. "Our practice continues to grow in the double-digits in terms of volume."

FIGURE 1

Stryker's Mako robot

Source: Stryker

CRITICS CITE HIGH COSTS

Other surgeons, however, say that during this critical time in health care when both hospitals and surgeons are trying to find new ways to cut costs and better manage their patients and improve outcomes – a theme that was widely discussed at this year's AAOS conference – introducing a costly piece of capital equipment is counterproductive. *(Also see "Total Joints: Bundled Payments Driving Procedural Innovation" - Medtech Insight, 26 Apr, 2016.)*

Roger Freeman, a veteran orthopedic surgeon in San Diego, believes that most experienced orthopedic surgeons can achieve the same results, in terms of patient outcomes and satisfaction, without making the significant capital investment in robotic technology.

"I think while the Mako robotic system may provide slightly better accuracy during a total knee replacement surgery, it is questionable whether it would lead to a significant improvement in patient outcomes," Freeman told *Medtech Insight*.

Wells Fargo analyst Biegelsen noted that convincing these critics would require Stryker investing in more clinical trials: "Generating peer-reviewed data will take several years, because SYK would have to enroll the study and journals typically do not publish data with less than two years of follow-up. In the interim, we would expect individual surgeons or sites to publish their data and talk about their anecdotal experience," he wrote in his Mar. 16 note.

ZIMMER BIOMET, S&N TOTAL KNEE ROBOTS AT AAOS

While Mako's total knee replacement system fed the main buzz at AAOS, two other orthopedic giants, **Zimmer Biomet Holdings Inc.** and **Smith & Nephew PLC** were trying to divert surgeons' attention to their own respective robotics-assisted total knee arthroplasty systems at the expo.

Zimmer Biomet displayed its robot for total knee based on the *Rosa* robotic platform it acquired as part of the **Medtech SA** acquisition *(Also see "Deals Shaping the Medical Industry, August 2016" - In Vivo, 4 Aug, 2016.)* last summer at its booth. The *Rosa Brain* and *Rosa Spine* received US FDA clearance in December 2015 and January 2016. The company said it expects to file for FDA clearance of its total knee robotic system in 2018, with an expected launch data of 2019. (See Figure 2.)

FIGURE 2

Zimmer Biomet's Rosa robot

Source: Zimmer Biomet

Louis-Phillippe Amiot, VP and GM of Zimmer Biomet's Personalized Solutions, told *Medtech Insight*, that the Rosa system provides surgeons with repeated measurements during the surgery that preserve speed and accuracy while assisting surgeons with joint stability.

When asked what makes the Rosa total knee system different from Stryker's Mako total knee system, Amiot said, that "At the moment, they (Stryker) are focusing a lot on the bone cuts, and they are talking about the stability of the articulation, but I think this is the first time a machine (Rosa) will really be used to evaluate and optimize the stability of the procedure – you have all the other benefits – accuracy of the bone cuts, etc., etc. – but you get the added benefit of a real physiological test to assess the stability of the articulation."

Another industry giant, Smith & Nephew, also hosted live hands-on demos of its *Navio* hand-held robotics-assisted total knee arthroplasty (TKA) system at its booth. The company made its move into the robotics space with the $275m acquisition of **Blue Belt Technologies Inc.**[See Deal] in 2015. Navio integrates intelligent instruments with CT-free registration and a patient-specific planning process that enables precise and reproducible resection of bone and soft-tissue balancing during implant procedure, *Medtech Insight* reported earlier.

According to Wells Fargo's Biegelsen, Stryker believes it has a significant head start on the competition, because "the development of the Mako total knee application began in 2009, well before Stryker acquired **MAKO Surgical Corp.**[in a $1.65bn deal in 2013]."

The analyst also said that Stryker's "management admitted that getting the total knee application to this point has taken longer and cost more money than expected. Management also believes it has strong IP protection."

Given its experience in bringing the Mako total knee to market, Biegelsen said Stryker is "skeptical of the timeline that ZBH can deliver on its plan to launch its robotic total knee in early 2019."

SMALLER RIVALS LOST IN THE HYPE

Meanwhile, Biegelsen noted that somewhat lost in the hype of the Mako launch and the competitive responses are smaller companies, such as **OrthAlign Inc.** and **OrthoSensor Inc.,** which are trying to improve total joint replacement patient outcomes at a significantly lower cost compared to robots.

Privately-held OrthAlign offers a handheld navigation device, *KneeAlign*, that provides an intraoperative alignment tool without disrupting the surgeons' typical workflow. The technology targets surgeons that want to use a tool providing real-time feedback, but at a much lower cost than a robot.

OrthoSensor offers a disposable device for total knees, allowing surgeons to intraoperatively make decisions on implant position and soft-tissue releases to improve knee balancing, according to the research report. In peer-reviewed studies, OrthoSensor showed 97% of patients whose knees were balanced using this technology were satisfied to extremely satisfied vs. 81% after a total knee without the technology.

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GE Healthcare Patches In Wireless Fetal Monitoring Device

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GE Healthcare will be rolling out worldwide *Novii, a* wireless maternal and fetal mo nitoring device it has gained through its acquisition of Monica Healthcare, a company spun out from the University of Nottingham in the UK.

Novii is a single-use stick-on patch that picks up the maternal and fetal heart rates, as well as uterine activity simultaneously, then communicates this information wirelessly through Bluetooth to the fetal monitor. The technology uses electrophysiological signals that can be passively detected by electrodes on the patch, which is positioned on the maternal abdomen. The patch is frequently used with mothers with high body mass index (BMI), with whom it is challenging to get accurate readings for both maternal and fetal heart rates.

GE Healthcare and Monica are no strangers, with GE being Monica's North American distribution partner for Novii since 2015. GE will now be taking steps to expand distribution across several terrorities. "Right now Novii is not being sold anywhere else than the US and that's one of the great benefits of GE Healthcare, we have a specialized distribution team in almost every single country across the world and most of these teams are anxious to get their hands on this product," Tammy Noll, general manager of GE Healthcare's Maternal Infant Care business told *Medtech Insight*."

Noll said the company aims to capitalize on the specific benefits the device brings when used on high-BMI mothers by targeting and growing this segment in the US and abroad. "Australia is one area we plan to target as [the expectant mothers in this country] has BMI percentages simi lar to the US. The second one is Europe because although [expectant mothers in this region] has a lower BMI compared to the US, it has increased in the last decade in certain countries like the UK, which we will also be targeting."

Photo credit: GE Healthcare

Monica Healthcare's technology is in use at approximately 1000 sites in Europe, Asia and North America and over 100,000 patients reported to have used it last year.

The acquisition expands GE Healthcare's maternal infant business further as it gears up to meet increased demand for neonatal and fetal care equipment worldwide. According to a recent report by Grandview Research, the global market for fetal and neonatal care equipment is valued at $6.7bn and is expected to expand by nearly 8% by 2025. "Right now we are a very good maternal, fetal and neonatal company and Monica Healthcare helps us with that," said Noll. "However, in the future we would really like to be a perinatal solutions company looking at [patients after discharge] and following the entire patient pathway so we'll need to add in and consider all options to accomplish that."

Noll added: "The maternal fetal monitoring space and clinical delivery has not changed in decades and practice has stayed the same for a long time. Everything around us is moving to become wireless and digital and what Monica Healthcare has been able to develop is unique, disruptive, transformational technology which moves fetal monitoring devices to the digital era. The technology they've developed is light years ahead of what is out there today."

Financial terms of the deal were not disclosed but is believed to have generated returns of 3.5x for the East Midlands Regional Venture Capital Fund, managed by Catapult Ventures – an early investor in Monica. GE Healthcare will retain Monica Healthcare's facilities in Nottingham and also acquire Novii's predecessor product, a wired fetal monitor *Monica AN24*, which is currently sold primarily outside of the US.

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SURTAVI Supports Intermediate-Risk Intervention For Medtronic's CoreValve

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Two-year results of the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial show that transcatheter aortic valve replacement with **Medtronic PLC**'s *CoreValve* or *CoreValve Evolut R* is noninferior to surgical valve replacement in patients with aortic stenosis at intermediate risk of complications during surgery.

"We made our two-year non-inferiority endpoint with very strong statistics," SURTAVI's lead investigator, surgeon Michael

Reardon of Houston Methodist DeBakey Heart & Vascular Center, told *Medtech Insight*. Reardon presented the results at the American College of Cardiology Annual Scientific Session in Washington, DC on Mar. 17. The data was also published simultaneously in *The New England Journal of Medicine*.

The rates of all-cause mortality or disabling stroke at two years were similar in patients randomized to treatment with one of Medtronic's self-expanding transcatheter valves as the rates in the patients randomized to surgical aortic valve replacement (SAVR) – 12.6% for TAVR versus 14.0% for surgery, meeting the threshold for statistical noninferiority with posterior probability of more than 0.999.

The surgery patients had higher rates of acute kidney injury, atrial fibrillation, were more likely to need a blood transfusion, and the surgery patients had to stay in the hospital longer than the TAVR Patients. However, the TAVR patients had higher rates of residual aortic regurgitation and need for pacemaker implantation. The TAVR group also ended-up with a lower mean pressure gradient across the valve and larger aortic-valve areas than the surgery group. Neither group showed valve deterioration at 24 months.

In SURTAVI, 5.3% of patients in the TAVR group experienced moderate-to-severe paravalular leak at one-year and 25.9% of the TAVR patients needed a pacemaker.

Medtronic will submit these results to the US FDA to support an expanded indication for its TAVR systems, which are currently only approved for patients at high or extremely high risk during surgery. FDA has already approved **Edwards Lifesciences Corp**'s *Sapien XT* and *Sapien 3* TAVR systems for intermediate risk patients based on results of the PARTNER IIa trial and the Sapien 3 observational study *(Also see "US FDA Approves First Intermediate-Risk Indication For TAVR" - Medtech Insight, 18 Aug, 2016.)*.

On Mar. 17, the American Heart Association and American College of Cardiology released a focused update of their valvular heart disease guideline stating that "after consideration by a heart valve team, TAVR is a reasonable alternative to surgical AVR for patients with severe, symptomatic aortic stenosis (stage D) and intermediate surgical risk." The AHA and ACC gives this recommendation a Class IIa rating, indicating that the "weight of evidence/opinion is in favor of usefulness/efficacy." But Reardon believes that, now that the SURTAVI results have largely confirmed the PARTNER IIa results, the ACC and AHA will soon reclassify this recommendation as Class I, the highest recommendation, which specifically indicates "conditions for which there is evidence, general agreement, or both that a given procedure or treatment is useful and effective."

Medtronic's CoreValve transcatheter aortic valve in situ

ANOTHER INDICATION EXPANSION SOON

Reardon pointed out that the survival rates of the SAVR patients in SURTAVI were about twice as good as that of the surgery groups in any other randomized TAVR trial, including the PARTNER IIa. *(Also see " Expanded Indication For Edwards' Sapien 3 Squarely In Sight " - Medtech Insight, 6 Apr, 2016.)*

The SURTAVI patients were slightly less ill overall than the PARTNER IIa patients, with a Society of Thoracic Surgeon score of 4.5% in SURTAVI vs 5.4% in the PARTNER IIa. "So despite the best surgery [results] we've ever seen, TAVR stayed toe-to-toe," he said.

"That's not because we're such great surgeons, but because we recruited a patient mix that is slightly less risky than PARTNER IIa. Each one these trials has moved a little bit down the risk scale," Reardon said. "This one was at the lower end of intermediate risk whereas [PARTNER IIa] was at the upper end. And what that does is it gives us some confidence that as we move toward lower-risk [patients], we're still doing very well, despite the fact that as you go to the lower-risk it should be harder for us to compete with surgery."

"The downside to TAVR in all of the trials so far are really three big things: paravalvular leak, pacemakers, and durability," he said. The ten to 20-year durability of TAVR valves is not known yet because they're still too new, but new surgical valves are enthusiastically adopted by surgeons without long-term durability data either, Reardon said.

He pointed out that 84% of the TAVR patients in SURTAVI were treated with Medtronic's first-generation CoreValve and 16% got the CoreValve Evolut R and the clinical results from Europe and the US show that CoreValve Evolut R produces lower rates of paravalvular leak than the first generation CoreValve. *(Also see "TCT 2015: More TAVR Results, Super-Thin Strut Stents, And Percutaneous Heart Pumps" - Medtech Insight, 29 Oct, 2015.)* Also, initial results from 60 patients treated with Medtronic's third-generation *CoreValve Evolut Pro* system, presented at the ACC meeting on Mar. 18 by John Kiene Forrest of Yale University, showed no paravalvular leak in 75% of patients, and only mild paravalvular leak in the other 25%. "So that's an engineering problem that we're rapidly fixing."

The need for pacemakers has been more of a problem for Medtronic's self-expanding TAVR valves than Edwards Sapien valves, which are balloon-expandable. Reardon explained that TAVR patients sometimes need a pacemaker because the heart's atrioventricular node, which coordinates the contraction of the ventricles, is right below the aortic valve below the membranous septum. "As a surgeon, I can see the white fibrous septum and then the red muscle below that where the [AV node] runs and I can avoid it with my sutures," he said.

"But the lower we put these [TAVR] valves, the more likely they are to push on this, and therefore cause pressure and node-dysfunction, especially in older people who don't have great nodes to begin with," Reardon explained. "But one of the nice things about the Evolut is because its recapturable/repositionable/redeployable, you have a little more confidence

to deploy it high, because if you deploy it high and it pops out, it's no big deal. You just recapture it and put it in again. So as we get into better and better engineering of the valve we'll get that taken care of."

About 28% of patients in the original CoreValve high-risk study needed a pacemaker after their TAVR procedure. *(Also see "ACC 2016 BEST OF THE REST: Surgery Trials, More CoreValve Data, Leadless Pacemakers, Drug-Filled Stents, And More" - Medtech Insight, 7 Apr, 2016.)* But the rate of patients needing pacemakers with CoreValve Evolut R is about 12-16%, which is lower than that in CoreValve patients and the data on preliminary CoreValve Evolut Pro data shows a pacemaker-implant rate of just 10%, Reardon said. "So we feel like we're gaining on that ground too," he said. "So there are still downsides to this, but a lot of the downsides have engineering solutions to them we're getting better rapidly."

Both Medtronic and Edwards are running trials comparing TAVR to surgery in low-risk patients and Reardon anticipates that TAVR will be able to match SAVR's performance in those trials too. But even if TAVR is indicated for the whole risk-spectrum, many patients will still need to undergo open surgery to get a new valve.

For example, patients with bicuspid aortic valves – a structural abnormality in which two of the valve's three leaflets have fused – have been excluded from all the TAVR trials and at least 20% of patients over 80 with aortic stenosis have bicuspid valves and bicuspid valves are even more common in younger patients with aortic stenosis. Some anatomies, such as patients with extensive left-ventricular outflow calcification are easier to treat with TAVR, and some patients need multiple structural heart repairs simultaneously that can be done during an open-heart surgery but not with a transcatheter procedure.

"Surgeons are worried that everyone is going to get a TAVR valve and that's just absolutely not true," he said. "What's going to happen is that we sit down as a heart team and decide what's best," he explained. FDA, the professional cardiology societies, and third-party payers have been pushing hospitals to create heart teams – with both surgeons and interventionalists – to make joint decisions about recommendations for heart valve patients since the FDA approved the first TAVR system about five years ago. *(Also see "Sapien Heart Valve Gets FDA Panel Nod For High-Risk Surgical Patients" - Medtech Insight, 18 Jun, 2012.)*

COMPETITION HEATS UP

Commenting on the results in a Mar. 17 note, Wells Fargo analyst Larry Biegelsen wrote that the SURTAVI outcomes were about what he expected, but TAVR was only non-inferior to surgery in the trial, as opposed to superior, because the surgery group had better outcomes than anticipated, "While some may be disappointed that TAVR was not superior to SAVR in SURTAVI, we believe the SURTAVI results are still impressive for TAVR given how well SAVR performed in the trial," Biegelsen concludes.

"We would expect Edwards to highlight the data showing that Sapien 3 was superior to SAVR in the PARTNER IIa trial and Medtronic will likely counter that that was a propensity-matched analysis, not a true randomized control trial," he said.

The 5.3% moderate-to-severe paravalvular leak rate in the SURTAVI TAVR group compares unfavorably to the 1.5% rate with Sapien 3 after one year in the PARTNER IIa trial. Also the 25.9% pacemaker-implant rate in the SURTAVI TAVR group is over twice that seen with Sapien 3 in PARTNER IIa. "While we would expect Edwards to market against CoreValve/Evolut R with this data, we would note that Medtronic's Evolut Pro should help reduce the paravalvular leak rate," Biegelsen explains. The company expects to launch Evolut Pro in the US in the by the fall of 2017.

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When Surgical Robotics Become Wearable

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A pan-European team of researchers developing what they believe to be the first wearable robotic system for surgery has won a €4m grant from EU's Horizon 2020 research and innovation program. The technology, which includes an exoskeleton glove that surgeons wear to remotely operate surgical instruments inside the patient, is expected to overcome challenges of current generation surgical robotics, like **Intuitive Surgical**'s market-leading *da Vinci* system, and offer far more flexibility so surgeons can perform more complex minimally invasive procedures faster and with more effective outcomes.

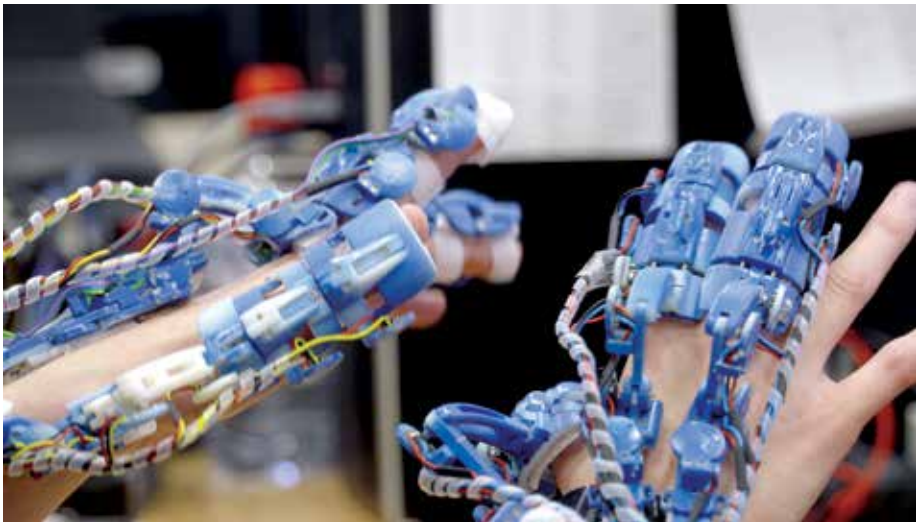

Photo credit: UWE Bristol

The €4m will be shared among the 10 partner organizations involved in the project and will take the technology through to *ex vivo* animal studies around three years from now, *Medtech Insight* has learned. Leading the project is Sanja Dogramadzi of the Bristol Robotics Laboratory (BRL), a collaboration between the University of the West of England and the University of Bristol, and the UK's largest robotics lab.

Dogramadzi explained to *Medtech Insight* that each of the 10 project partners are responsible for different aspects of the initiative: "Some partners are surgeons, the end-users of the technology, and they will provide us with user requirements. Some are commercial partners, who are interested in commercializing the technologies that emerge from this project." Then there are three academic partners, including BRL, that are responsible for different aspects of R&D. BRL will be in charge of designing the surgical instruments used on the patient and the sensing components of the technology, added Dogramadzi. "We also have a partner in Greece and in Milan, and they will be looking at vision and control, and the user interface between the surgeon and the robotics system."

There are three key components to the robotic surgical system. Firstly, there are the advanced surgical instruments that are used on the patient. These instruments, said Dogramadzi, would require "good articulation and good sensing of the environment." They would have haptic abilities that allow the surgeon to "feel" the tissue and organs inside the body, just like they would during conventional surgery.

Second, there is the exoskeleton, the "master" side of the system, that will fit over the surgeon's hands like gloves and will pick up data related to the positioning of the hands, enabling the surgeon to operate the surgical instruments remotely. The wearable exoskeleton will enable movement that is more intuitive, as well as give the surgeon the sense of touch; this would mean training surgeons on the use of the system would be easier, the researchers believe. Additionally, the sense of touch in this system will be dual: current research in haptic systems mainly focuses on the arm/forearm of the user, but the system developed in this project will focus on haptic feedback on the fingers of the surgeon as well, according to the BRL researchers.

The third component to this new robotic surgical system will be smart multifunctional glasses, worn by the surgeon, which will relay live images from inside the body, and provide a realistic view of what is taking place inside the body as the robotic tools are being used on the patient. By pairing the exoskeleton with the smart glasses, this gives surgeons the flexibility to position themselves anywhere in the operating theatre, Dogramadzi told *Medtech Insight*. "They can be closer to the patient; they can sit in another room. There are no limitations," she said. These advances offer an improvement over current systems like the da Vinci, which uses a large, installed master console with a flat TV screen for visuals. This console cannot be moved easily and the doctor is removed and detached from the patient.

Dogramadzi acknowledged that there will be technical challenges ahead, a significant one being to strike a balance between making the surgical instruments capable of performing complex procedures, while keeping them simple for the surgeons to operate. Another is ensuring that the haptic capabilities, which the wearable system are expected to offer, will indeed help the surgeon perform the procedure better and more safely. "We're hoping to develop the surgical instruments so they have sensing capabilities and the surgeon will have haptic feedback from the instruments inside the body. So, we're trying to define and analyze the surgical operation that they are doing, and where the safe and critical parts of the procedure are to see where the haptic feedback is needed. Rather than developing the haptics for two or three fingers, per se, we are developing the haptics to ensure surgeons can safely manipulate the instruments inside the body during the whole procedure, and that they don't make cuts or ruptures where they shouldn't."

Work on the project had already begun in January and the researchers are now at a stage where they are looking at the requirements for certain surgical procedures – procedures which the surgeon currently are not able to or have great difficulties performing accurately, safely and in a short period of time, Dogramadzi said.

"Currently, the da Vinci system is used quite a lot in urology. It is very good for prostate removal, for example. But if you want to do other procedures in that region of the body, da Vinci has its limitations, so we're talking to surgeons to understand what these limitations are and how to improve on the technology," she said. "da Vinci was actually developed from industrial robots, so [that platform technology] is a bit old school. The field of robotics has moved on so much since; we can achieve better control, we have better materials, we can design robots a lot smaller. So, we are trying to exploit these advancements so existing procedures can be improved and also open up new procedures for robotic surgery."

These new procedures would likely be in cardiovascular surgery, where the robots are still rarely used – if at all – and many heart and vascular surgical procedures are still invasive. Another area that the researchers are exploring is in arthroscopy, and using robotics to better restore soft tissue in knee joints, for example.

By developing the wearable surgical robotic system so that it addresses these surgeons' needs, Dogramadzi the technology can "benefit the patient, the surgeon and the health provider. If you can use this system to perform a surgical procedure that has 100% rate of success, patients recover faster, the surgeons can also perform it faster so more procedures can be performed per day, and there will be great improvement for all sides."

With the €4m Horizon 2020 funding taking the project to *ex vivo* animal studies – three years from now – Dogramadzi estimates that it would likely take yet another three years for the technology to be ready for clinical studies.

CLICK

To find out more about other research conducted on cutting-edge surgical robotics, read "Ever Decreasing Dimensions, Snakes And Origami: The Next-Gen Surgical Robots." http://bit.ly/2lvARNh

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Pulse Biosciences Shoots For US Clearance Of Nano-Pulse Platform

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Pulse Biosciences Inc. expects to begin a pilot study of its *PulseTx* nano-pulse system for immunoncology applications within a year, building on preclinical research showing that very short pulses of electricity can both induce cell death without residual tissue damage and induce an immunologic response that prevents cancer from coming back.

"I think the year ahead was really about clinical development," Darrin Uecker, CEO and president of Pulse Biosciences, told *Medtech Insight*. "We spent the last 12 to 18 months developing a platform and now we think we can leverage that platform as we go out into different application areas."

Direct current pulses of hundreds of volts lasting hundreds of microseconds have been used in various applications to create holes in cell walls, but in 2001, researchers at Old Dominion University in Norfolk, Virginia, showed that nano-pulses – small bursts of electrical current lasting about ten nanoseconds – applied to white blood cells could create holes in the outer cell membrane as well as organelles inside the cells, which stressed the endoplasmic reticulum enough to trigger apoptosis (programmed cell death), Uecker explained. Unlike other types of tissue ablation that "blow-up" the cells, the nano-pulse approach did not create secondary inflammation or lasting damage beyond the target cells.

Subsequent research of the effect of 300 nanosecond 40kv/cm pulses on melanoma cells showed that the pulses penetrated into the interior of every tumor cell and initiated DNA fragmentation and apoptosis while at the same time reducing blood flow to the tumor. In 2014, research led by Ru Chen at Old Dominion showed that liver cancer cells in rats could be destroyed with nanosecond pulsed electric fields with 80-90% response rate and that the successfully ablated tumors did not regrow because the nanopulses were triggering an anti-tumour adaptive immune response. This finding "opened the door into a whole other area of research into what is happening to the immune response," Uecker explained.

PulseTx creates nanopulses of electric current that induce cell death an adaptive immune response.

Photo credit: Pulse Biosciences Inc.

"It's going to be very interesting, in terms of a continuum of care as it relates to immunoncology," he said. "We are, from a mechanistic point of view, on the front end of that spectrum. Our device looks like an immune-priming technology so that when we treat a tumor of a certain type, we're really exposing the antigens from that tumor to the immune system," he said. "There are a lot of other technologies that look to do that kind of thing, like oncolytic viruses and other things, but we think that technology like this, which is very focal and doesn't add drug-toxicity or anything like that, is very exciting and very synergistic with a lot of the activities going on in immunoncology."

The pilot trial will test PulseTx in treating melanoma. "It represents a very good model from a clinical study prospective to demonstrate what our technology does," Uecker said. "It's a multifocal disease and will allow us to treat the disease and see and measure the immune response."

The company is also developing PulseTx for cosmetic dermatology treatments and has launched a dose-response study evaluating the effects of the nanopulse therapy on healthy skin. Because PulseTx can be targeted so precisely, it could be an improvement over technologies that remove skin lesions by freezing, burning, or cutting them off and often leave a scar.

"We think this technology is going to be really interesting for being able to remove many different types of benign lesions with a cosmetic result which is going to be very favorable for the patient," he said. "This initial dose-ranging study is really an effort to guide us down that path by informing us about the disruption and healing that you get from this technology in healthy skin." On Mar. 14, the company announced that it has successfully completed patient treatments and follow-up visits in the dose-response study with "positive interim results."

Pulse Biosciences also announced Mar. 14 that it filed for a 510(k) with the US FDA for a general soft-tissue ablation indication. Obtaining this general indication before adding more specific therapeutic indications is a well-worn regulatory path for ablation technologies, Uekcer said.

In its financial results for the fourth-quarter and full-year 2016, the firm disclosed it had cash equivalents and investments totaling $16.4m, as of Dec 31, but added $5m of additional capital in February. In that private placement, Robert Duggan and Maky Zanganeh, the former CEO and COO of **Pharmacyclics Inc.** – now part of **AbbVie Inc.** – purchased $5m worth of shares directly from the company and $5m from other shareholders. Duggan and Zanganeh now have a 17.1% interest in the company and Zanganeh is on the company's board.

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