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MIS 2017

‘Artificial pancreas’ takes No. 1 spot in Cleveland Clinic’s Top 10

By Jennifer Boggs, Managing Editor

CLEVELAND – A technology so promising it took the FDA barely 100 days to clear it for marketing approval topped the Cleveland Clinic’s list of 10 innovations expected to have significant impacts on health care in 2018. Unveiled on the last day of the 15th annual Medical Innovation Summit, the list leads with the closed-loop insulin delivery system for type 1 diabetes and includes advances such as gene therapy and telehealth that have been years in the making.

See Top 10, page 3

Inside

MIS 2017

Surgical robotics becoming a staple in health care industry

By Omar Ford, Staff Writer

CLEVELAND – Surgical robotics figure prominently in med-tech innovation, said members of a panel at the Cleveland Clinic’s 2017 Medical Innovations Summit. A session titled, “Maps, models, and robots: How med-tech is personalizing surgery,” was a slight departure from the summit’s overall theme of Genomics and Precision Medicine.

The CEO’s of both Intuitive Surgical Inc. and Stryker Corp. weighed in on how robotics have become relevant in med-tech.

“I think robotics are here to stay,” said Kevin Lobo, chairman and CEO of Stryker. “A couple of years

See Robots, page 4

Medtronic starts the first U.S. pivotal trial for transcatheter mitral valve replacement

By Stacy Lawrence, Staff Writer

Enabling the gradual transition from open-heart surgery to more minimally invasive procedures is a long-standing medical device industry effort. The latest advance on that front could be transcatheter mitral valve replacement (TMVR) therapy. Dublin-based Medtronic plc has now staked a claim to being the first to start a U.S. pivotal trial in this field, adding to the prior advancements in transcatheter repairs of the mitral valve.

The study will test the Intrepid TMVR system, which Medtronic gained from its 2015 acquisition

See Medtronic, page 6

MDR tougher than FDA

EU sets high bar for clinical data required for every CE marked product

By John Brosky, Contributing Writer

BERLIN – The reform of rules governing the CE mark has shifted requirements for clinical evidence from nearly nothing to far more than most manufacturers can readily provide.

No product sold in the EU is spared as the law does not allow for the grandfathering of any of the estimated 500,000 products already on the market.

Passed into law in May 2017, the rules fully apply in May 2020 after a transition period that will

See CE mark, page 5

Regulatory

Final 510(k) changes say QSRs can help avoid new submission

By Mark McCarty, Regulatory Editor

The final FDA guidance for determining whether a change to a class II device requires a new 510(k) may be the most important guidance of the year, but the most important part of the final 510(k) changes guidance may be that it states that

See FDA, page 7

Appointments and advancements

Baylis Medical Co., a Mississauga, Ontario-based developer of interventional cardiology products, reported its president and co-founder, Kris Shah, has been named to the **Advanced Medical Technology Association**'s (AdvaMed) Accel board of directors.

The Medicrea Group, Lyon, France-based provider of the Unid adaptive spine intelligence (ASI) digital health care platform, said it has hired Joseph Walland as executive vice president of U.S. sales and Richard Washburn as executive vice president Unid ASI to support its new business development model in the U.S., effective Oct. 23, 2017. Walland served most recently as the western area vice president for Stryker Spine. Washburn joins Medicrea from Trice Medical, where he served as chief technology officer.

Synteracthcr Inc., a full-service contract research organization based in Carlsbad, Calif., reported the appointment of John Potthoff to its board, effective immediately. Potthoff is a founder and CEO of Elligo Health Research, a clinical research infrastructure provider. He currently sits on the board of directors for Chesapeake IRB and previously served as a member of the board of directors for Chiltern.

Tekni-Plex Inc., Wayne, Pa.-based producer of packaging materials, medical compounds and tubing, promoted Glenn Fish to chief operating officer. Previously, Fish was chief financial officer and executive vice president. He has been with the company for three years.

Financings

San Diego-based **Nuvasive Inc.**, a spine technology firm creating minimally disruptive, procedurally integrated solutions, reported its board of directors approved a share repurchase program authorizing the purchase of up to $100 million in common stock over a three year period beginning Oct. 25. As part of the program, the firm can repurchase stock periodically as the company deems appropriate, and subject to legal and market conditions. Repurchases can be executed using open market purchases, privately negotiated purchases or other transactions, and are expected to be funded by cash available, operations cash, or credit facility borrowing.

U.K.-based **Quotient Ltd.**, a commercial-stage diagnostics company, reported it has entered a private placement agreement expected to garner $40 million gross, and an additional $49 million prior to July 31, 2018, with full exercise of the warrants. Proceeds are planned for development, corporate counsel, scale up and possible commercialization of Mosaiq. The agreement includes 7,864,683 ordinary shares at $4.64 per share; 550,000 prefunded warrants at $4.755 per underlying prefunded warrant exercisable for up to 550,000 ordinary shares at $0.01 per ordinary share; and 8,414,683 warrants at $0.125 per underlying warrant share exercisable for up to 8,414,683 ordinary shares at $5.80 per ordinary share.

Product briefs

Chicago-based **Attune Medical** received notification from the U.S. **FDA** that it has cleared the EnsoETM (esophageal temperature management) device for an extended duration of use for up to 72 hours. The EnsoETM is the only patient temperature management system cleared for use in the esophageal environment for whole-body temperature modulation, including both warming and cooling.

Capsovision Inc., of Saratoga, Calif., reported CE mark approval for its Capsocam plus system in patients ages 2 and above. It is the only wire-free capsule endoscopy system on the market that provides a 360 degree panoramic lateral image of the small bowel mucosa.

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Top 10

Continued from page 1

To compile the list, 150 to 200 Cleveland Clinic physicians from across the different institutes, along with 20 to 30 venture capitalists and a few members of the media were interviewed for their suggestions, explained Michael Roizen, chief wellness officer. An initial list of 300 to 400 suggestions was culled to 150, with two groups of physicians meeting to whittle that number down to 10.

There were two primary criteria, Roizen said. Any technologies or therapeutic approaches to make it on the list had to be innovative and be expected to change patient care in a major way in 2018.

1. Keeping patients in the loop

"Trying to control diabetes is a challenge for many patients," said Jim Young, chair of the Endocrinology & Metabolism Institute. Patients with type 1 diabetes, in particular, have to continuously monitor their glucose levels throughout the day, manually giving themselves insulin – via injection, pen or pump – to avoid becoming hyperglycemic. Even those that opted for the more convenient pump still had to suffer multiple finger pricks daily and had to program the device.

Last year, the FDA approved the first hybrid closed-loop insulin delivery system, Medtronic plc's Minimed 670g, after barely three months of evaluation – "that's unheard of," Young said. Often called an artificial pancreas – the name is a bit of a misnomer, since the pancreas is responsible for more than insulin production – the closed-loop technology was launched earlier this year.

It's designed to enable direct communication between the continuous glucose monitoring device and insulin pump to adjust insulin levels with little to no input from the user. That represents a "dramatic change," Young said. "We've been trying to develop closed-loop systems for many things and this is really an example of the first and best to come on board."

So 2018 should see the closed-loop system really disrupting the diabetes market, as more patients demand access and more insurers reimburse for the system.

In addition to being more convenient for patients, it also should better manage HbA1c levels and that should "translate into improvements in mortality and morbidity in the diabetes population," Young said. "I think it's an explosive technology that's going to get out there big and fast."

2. A good night's sleep

For the 21 million Americans with sleep apnea, continuous positive airway pressure (CPAP) devices are the standard treatment; however, patients often complain of the noise, bulkiness and irritation of nightly use, making compliance a problem. Estimates indicate that more than 40 percent of patients refuse to wear their CPAPs as instructed.

And sleep disorders are on the rise, said Tina Waters, of the Sleep Disorders Center. When people go without treatment that "increases their risk of having a lot of underlying diseases" and complications.

In sleep apnea, the airway muscles lose ability to stay open, allowing air into the lungs. "They get floppy, so to speak," Waters explained.

Now there's an implant, inserted via a minimally invasive procedure, which can be controlled by a remote or a wearable patch, that can deliver stimulation to open airway muscles during sleep. Acting in a similar way to a pacemaker, the implant helps synchronize the intake of air with the action of the tongue using a breathing sensor and a stimulation lead powered by a small battery. Respicardia Inc. received FDA approval for its Remedē system for central sleep apnea in early October 2017. The implantable device stimulates the phrenic nerve automatically to impact the diaphragm while a patient sleeps. (See *BioWorld MedTech*, Oct. 10, 2017.)

3. Eyes on the prize

Earlier this month, the FDA's Cellular, Tissue and Gene Therapies Advisory Committee unanimously recommended approval of Spark Therapeutics Inc.'s BLA for Luxturna (voretigene neparvovec) in RPE65-mediated inherited retinal disease. The final FDA decision is expected in January, which would allow marketing of the first gene therapy for inherited retinal diseases.

The therapy is designed to deliver, via viral vector technology, a new "normal" copy of the gene to retinal cells, resulting in a functional protein. In clinical trials, it demonstrated the ability to improve visual function in some patients with RPE65-mediated diseases such as Leber congenital amaurosis and retinitis pigmentosa, rare genetic conditions that result in progressive vision loss and blindness.

Assuming the therapy clears the FDA, all eyes will be on the success of its use in patients in postmarketing data. Early approvals of any class of medicine are always important for the ones that follow, noted Aleksandra Rachitskaya, of the Cole Eye Institute.

"This is really affecting all areas of medicine," she added. "There are so many applications to the FDA for gene therapy."

4. How low can you go?

The unprecedented reduction of LDL cholesterol has made headlines in the past year. The addition of PCSK9 inhibitors – an entry on the 2015 Cleveland Clinic Top 10 list – to other treatments has shown a 20 percent reduction in the risk of cardiovascular death, myocardial infarction or stroke in recent studies. And that could be just the start. The drug combination has been shown to reduce low-density lipoprotein by as much as 75 percent. But in the past, doctors have been hesitant to get patients below the 35 percent mark, fearing neurocognitive side effects, said Leslie Cho, of the Heart & Vascular Institute.

"We now know it's safe without neurocognitive deficits," she said, while lower LDL levels also result in fewer cardiovascular events. She called it a "revolutionary thought process in cardiology."

In the future, physicians could look at a combination of statins and other drugs, with the addition of a PCSK9 inhibitor to

See Top 10, page 8

Robots

Continued from page 1

ago they were saying why robotics. Now they're saying which robot."

Kalamazoo, Mich.-based Stryker, well-known for orthopedics, made the decision to enter into the world of robotics when it acquired Mako Surgical for about $1.65 billion in 2013. (See *BioWorld MedTech*, Sept. 26, 2013.) Mako makes robotic assisted orthopedic surgery systems. The company sells the Rio robotic arm interactive orthopedic system and the Restoris family of implants to enable its flagship Makoplasty partial knee resurfacing procedure for the treatment of early to mid-stage osteoarthritis.

"[Robotics] allows for personalization of surgery," Lobo said. "It allows for preoperative planning; dynamic joint surgery; and dynamic visualization."

In March of this year the company launched its total knee replacement solution using the Mako robot.

"We're very bullish on the technology," Lobo said. "There are a lot of outcomes and variability today, and we believe [the Mako robot] will standardize those numbers."

Debbie Wang, an analyst with Morning Star, said in a research note that "Stryker management has demonstrated an acute understanding of new opportunities for med-tech competitors that have arisen thanks to the shift toward value-based reimbursement that has squeezed providers."

Wang added, "We anticipate Stryker will continue to make strategic acquisitions of technology and products that aim to avoid complications or cut costs."

Lobo said in the future he believes the robots will be smaller and more adaptive to the surgeon.

Robotic landscape

Sunnyvale, Calif.-based Intuitive is considered the top surgical device maker with its Da Vinci robots. For years the company has gone relatively unchallenged in the U.S. market in the surgical robotics space. Morrisville, N.C.-based Transenterix Inc. received a nod from the FDA to market the Senhance surgical robotic system this year. (See *BioWorld MedTech*, Oct. 17, 2017.) This was the second FDA clearance of a surgical robotic system for abdominal entry since Intuitive received approval for the Da Vinci in 2000.

"There are smart people doing interesting things," Gary Guthart, president and CEO of Intuitive, told the audience. "Making things in the operating room that are extremely effective is really hard. It's resource intensive. So some of those companies out there will create great products and will be natural partners for a company like ours."

In the past few years, other firms have stepped up to the plate to enter into the surgical robotics market.

"While admittedly, Intuitive has a wealth of experience that will 'always' make it the gold standard in robotic surgery the entry of newer platforms is bound to chip away at incremental growth," Suraj Kalia, an analyst with Northland Capital Markets, said in a research note.

> *"I think robotics are here to stay. A couple of years ago they were saying why robotics. Now they're saying which robot.*
>
> Kevin Lobo
> Chairman and CEO, Stryker

Movements in Robotics

In 2016, Mountain View, Calif.-based Alphabet Inc.'s Verily Lifesciences LLC teamed up with New Brunswick N.J.-based Johnson & Johnson Corp.'s Ethicon unit. The companies formed Verb Surgical LLC, which is tasked with developing the surgical platform. Earlier this year, Verb demonstrated its first digital surgery prototype to both J&J and Ethicon executives. (See *BioWorld MedTech*, Jan. 27, 2017.)

In February, Medrobotics Corp., Raynham, Mass.-based maker of the Flex Robotic System, raised $20 million in preferred stock financing. (See *BioWorld MedTech*, Feb. 22, 2017). The financing allowed the company to further research an abdominal port entry for general, gynecological and urologic surgeries. The company won CE mark for colorectal use in 2014 and FDA clearance in 2015 for ear, nose and throat use.

Medtronic executives have since revealed plans to enter into the surgical robotics market. (See *BioWorld MedTech*, Feb. 23, 2017.) The Dublin-based company is expected to launch a surgical robotics system on a limited basis in specific countries towards the end of fiscal year 2018.

Lobo chimed in on competition in the robotics market and Stryker's overall plan for keeping itself current on the market.

"Given the safety profile and what's required in health care to get approval, we usually have very good insight into what's coming," Lobo said. "It's not like other industries like the consumer products where you can suddenly become blindsided."

Lobo added, "I think we see the signals early, and we ask whether we want to adopt that or acquire that technology and merge it into our platform." ♦

CE mark

Continued from page 1

find regulatory affairs personnel scrambling to assemble documentation for technical files, quality systems, postmarket surveillance and proof of compliance all the way down the supply chain.

Much is still not settled for the Medical Device Regulation (MDR). An implementation road map expected in June 2017 was distributed to stakeholders on Oct. 18, 2017, but has not yet been formally released for manufacturers.

Two dozen essential implementing and delegating acts still must be drafted and approved, and the devil lies in the details of these texts.

Yet requirements for clinical evidence are a certainty, and the guidance published by the European Commission in July 2016 as "MEDDEV 2.7.1 Rev 4 Clinical Evaluation," was largely adopted in the new law, providing manufacturers a road map for compliance under the MDR.

Speaking to a conference for authorized representatives of CE marked products non-EU companies, Graeme Tunbridge, group manager for devices regulatory affairs at the United Kingdom's Competent Authority, the Medicines & Healthcare Products Regulatory Agency (MHRA), said, "The best advice is to apply what you can now, to look to the Rev 4 document for guidance, which is the state of the art ahead of the Regulations."

Each country in Europe has a Competent Authority, and the MHRA has served as the lead in designing the delayed roadmap for implementation. (See *BioWorld MedTech*, Oct. 9, 2017.)

Hans-Heiner Junker is the senior international affairs manager for Munich-based, TÜV SÜD Product Service, arguably the largest Notified Body in Europe, the agency that reviews files and grants the CE mark.

Speaking at the RMD 2017 conference, he said, "Notified Bodies will not only look into the technical documentation regarding clinical evaluation, they will also take a deeper look into how manufacturers are preparing clinical evaluation, how they do this. How they do the clinical investigation, how they plan it. How they define the competences of the people in the clinical evaluation process."

"The review and assessment of the clinical evaluation performed by the manufacturer will take more time, that's for sure. Also the audit of the clinical evaluation process on the manufacturer's side will also take more time," he said.

Dario Pirovano, the senior regulatory adviser for the trade association MedTech Europe based in Brussels, Belgium, presented a list of unknowns and uncertainties about the MDR.

Regarding clinical evidence, he cited the language in the law calling for "sufficient clinical evidence" to support product filings.

"What is 'sufficient'?" he asks. "This is something that needs to be clarified and needs to be clarified soon. Does an acceptable level of clinical evidence differ across different device categories?"

"And what is meant by an independent expert?" he asked, adding to the growing list of ambiguities in the law.

"Manufacturers need to plan, to look into their portfolio and determine what they need. What they need to do for sure is a thorough analysis of what data they have collected during the life of current products in postmarket and clinical follow-up to see whether they have a reasonable story to tell to the Notified Body," he said.

Sarah Sorrel, a member of the board of the conference organizer, European Association of Authorized Representatives, was charged with presenting the topic of clinical evaluation under the MDR to the conference. Sorrel is also the president of Medpass International Sas, an authorized representative service based in Paris.

"We are in a huge period of uncertainty right now – an unpredictable, unreliable environment, which is very uncomfortable for businesses," she said.

There are all sorts of actors in play with the new regulations, manufacturers, Competent Authorities, Notified Bodies, each of whom will hold different ideas of what is "sufficient evidence."

"You will want to find out what kind of clinical evidence you need, and yet it is very difficult to get a consistent reading in Europe. You go to one Notified Body, they will give you one opinion; you go to another, and they will give you another opinion."

Compounding the confusion, she said, is an urgency for manufacturers to determine now if products are ready for a document review of clinical evidence throughout the entire lifecycle from development through marketing of products.

"The problem with clinical evaluations is that they require clinical data, and you don't invent clinical data. Clinical data often comes from clinical investigations. If you have ever done a clinical trial, then you know they are not planned in a minute, are certainly not performed very quickly, and they are extremely expensive.

"If products don't make it, often it will because of a lack of clinical data," she said of the future CE mark approval under the MDR.

"The first thing for any manufacturer right now is to be updating clinical evaluation procedures to comply with MEDDEV Rev 4. They should look at regulatory risk in terms of what the current clinical evaluation reports look like. There is a particular risk for Clinical Evaluation Reports that will be based on product equivalence, especially for high-risk implantable devices."

Regarding product regulatory strategy, she said, "some manufacturers may want to consider going to the United States market first."

"I know this is a shock," Sorrel said, as it reverses the tradition built over 25 years of manufacturers placing products in Europe to build clinical data before approaching the FDA.

For example, she said, "In the U.S. with a 510(k) route, it is still possible to use substantial equivalence, which is quite different from the EU's [new] strict equivalence requirements. In some cases it will be easier to get on the market with substantial equivalence with a 510(k) than to stay on the European market." ♦

Medtronic

Continued from page 1

of Twelve Inc. for up to $458 million. At that time, the medical device giant characterized it "best-in-class" with the deal coming amidst a flurry of minimally invasive mitral and tricuspid valve replacement and repair startup acquisitions. Twelve investors received $408 million up front, with the additional $50 million contingent upon a CE mark.

Irvine, Calif.-based competitor Edwards Lifesciences Corp. is in a 200-patient CE mark trial for its Cardiaq mitral valve replacement, which it acquired with the 2015 purchase of Cardiaq Valve Technologies Inc. for up to $400 million, with $50 million of that contingent upon a CE mark.

Medtronic's pivotal TMVR trial is slated to enroll up to 1,200 severe, symptomatic mitral valve regurgitation patients. Data from a pilot study for Intrepid will be reported next week at the Transcatheter Cardiovascular Therapeutics (TCT) in Denver, Colo.

Interestingly, the trial is split into two arms, one for patients who would be eligible for open-heart mitral valve surgery, but are not eligible for mitral valve repair, as well as those who are not eligible at all for open-heart surgery. The prior group will be a cohort of up to 650 patients, while the latter will be up to 550.

"One of the challenges with mitral regurgitation is that it may coexist with multiple comorbidities, and the condition can lead to heart failure," Sean Salmon, Medtronic SVP and president of the Coronary and Structural Heart division told *BioWorld MedTech*. "The two cohorts in our view represent different patient populations."

He continued, "We expect patients in the surgical arm to have fewer co-morbidities and be suitable for a mitral surgery (in the judgement of the local heart team at each investigating site). Patients in the nonsurgical cohort will likely have greater co-morbidities, and not be eligible for a mitral surgery in the view of the local heart team."

This clinical trial structure, therefore, allows Medtronic to investigate the Intrepid TMVR System in both the targeted population who are most likely to benefit and serve as the basis for a potential approval – as well as in a population that has a huge unmet need but may not thrive quite as well due to age and comorbidities.

Intrepid details

"The Intrepid system features a truly innovative dual-stent design and the trial will investigate its safety and efficacy in addressing severe symptomatic mitral regurgitation replacing the need for an open-heart procedure," said Martin Leon, director of the Center for Interventional Vascular Therapy at Columbia University Medical Center/New York-Presbyterian Hospital and national co-principal investigator of the trial, which is known as APOLLO.

Mitral regurgitation occurs when blood flows backward through the mitral valve and into the heart's atrium each time the left ventricle contracts. It can lead to heart failure or death without treatment.

> *"We expect patients in the surgical arm to have fewer co-morbidities and be suitable for a mitral surgery (in the judgement of the local heart team at each investigating site). Patients in the nonsurgical cohort will likely have greater co-morbidities, and not be eligible for a mitral surgery in the view of the local heart team."*
>
> Sean Salmon
> SVP and president, Coronary and Structural Heart division, Medtronic

The Intrepid TMVR system uses self-expanding, dual-stent technology with a replacement tissue heart valve. It is delivered via a catheter that is inserted between the ribs to enter the heart. It is then expanded within the mitral valve, with the frame attaching and fitting to the existing heart valve. The valve is comprised of bovine tissue.

Medtronic's Cardiac and Vascular Group is its largest business after the Heartware International Inc. acquisition – and one of its faster growing. Last quarter, it had almost $2.7 billion in revenues, up 5 percent from the same quarter a year earlier. It includes the Cardiac Rhythm & Heart Failure (CRHF), Coronary & Structural Heart (CSH) and Aortic & Peripheral Vascular (APV) divisions. Being able to compete in mitral valve replacement eventually could help to keep that momentum going.

Summed up David Adams, surgeon-in-chief of Mount Sinai Health System, and national co-principal investigator of the APOLLO trial, "This is the beginning of an important journey to establish a truly less invasive approach to treat severe mitral valve regurgitation in patients who are appropriate candidates for mitral valve replacement with a transcatheter technology that eliminates the need for open-heart surgery." ♦

Product briefs

Cheetah Medical Inc., a Newton Center, Mass.-based provider of noninvasive hemodynamic monitoring, said new research results were presented at the American Society of Anesthesiologists Annual Meeting in Boston. The aim of the study was to better understand the impact of unguided intraoperative fluids and associated patient outcomes following abdominal surgery, using a large administrative database. The researchers found that intraoperative fluids of 6 liters or more is independently associated with harm to patients with an increase in both complications and death. It is estimated that greater than 21 percent of patients undergoing major abdominal surgery receive more than 6 liters of fluid. In addition, the level of fluids given to the patient is primarily driven by hospital practice and not patient or disease factors. The analysis was based on 36,252 discharges from 393 hospitals.

FDA

Continued from page 1

adherence to the Quality Systems Regulations can allow a change to go through without requiring a new regulatory filing.

The August 2016 draft guidance, a second attempt to rewrite the so-called K97 memo, did not include language seen in a 2011 draft that would have drawn some fairly bright lines around the use of split and multiple predicates. The 2016 draft included a number of flowcharts to aid in determining whether the sponsor is liable for a new regulatory filing, and was released concurrently with a draft guidance for 510(K) software changes. (See *BioWorld MedTech*, Aug. 8, 2016).

The responses to the 2016 draft cited several concerns, with one trade association making the case that this document did not draw appropriate restrictions around the term "substantive change." However, industry was also not clear on how risk management would be applied across the entirety of the draft, although there was some variance in views on whether the FDA wants to see a device maker go farther back than one iteration in that design tree when assessing the risks associated with a given change of design. (See *BioWorld MedTech*, Nov. 14, 2016.)

A number of voices in industry and among consultants have previously argued that the QSRs can adequately manage many of the risks associated with a change of device design. The final guidance includes a discussion of this proposition – a discussion that is absent from the draft – stating that a reliance on existing quality system mandates "is the least burdensome approach to reasonably assure the safety and effectiveness of the changed device." The agency seemed intent on reminding device makers that the regulations pertaining to design controls and device master records are still firmly in place, however. The least burdensome discussion also is taken up generally in a separate section in the final, although this section offers little in the way of specifics.

Risk management discussion expanded

Both the draft and the final stipulate that the terms do not apply to regulatory considerations that may be unique to combination products, although the general principles are nonetheless applicable. Unlike the draft, the final discusses risk management explicitly, starting with the notation that terminology found in ISO 14971 undergirds much of the verbiage in the final (ISO 14971 is itself undergoing a revision, the draft for which is expected to emerge in 2019).

The FDA said the definition of a new risk incurred as a result of design changes is "a new hazard or hazardous situation that did not exist for the original device," assuming "the pre-mitigation risk level associated with the new risk is not considered to be acceptable."

The final goes on to state that a device change "could be considered to significantly modify an existing risk if it changes the risk score, risk acceptability category, or duration of risk."

Another section that is new for the final guidance addresses the role of testing (described parenthetically as verification and validation) in determining the need for a new 510(k). The guidance states that any unexpected results seen in routine verification and validation could reverse an initial determination that no new filing is needed, although the agency stipulates that the term "routine" means the verification/validation work done on the existing configuration. However, the FDA said that each change to device design must be evaluated separately from other changes when the intent is to change the design in more than one respect.

The agency more or less explicitly foreclosed the notion of having to compare the latest iteration of a device with anything other than its immediate antecedent. A section dealing with appropriate comparative devices states that a risk-based assessment of changes should be made to the most recently cleared device, which the final guidance refers to as the "original device." An original device can also be the legacy pre-Amendments device or the device as described in a de novo application, assuming no changes have been imposed on either of those filings.

Intended use dilemma laid to rest

The FDA said the guidance applies to manufacturing changes as well, but the document also provides a clear line between the definitions for the terms "intended use" and "indications for use." The concepts were sufficiently blurred in the views of some that the agency had floated the notion of collapsing the terms into one in 2011, although the proposition eventually was abandoned. The 510(k) changes guidance stated that a change in the indications for use does not necessarily reflect on intended use.

The guidance noted that changes to an indications for use statement "raise more agency concern than any other aspect of labeling," and that the majority of changes to the indications for use statement would trigger a need for a new regulatory filing. On the other hand, a significant concession is seen in that the removal of an indication for use from a label bearing several indications "would not likely require submission of a new 510(k)."

Among the other provisions in the final are that a device that was previously labeled as reusable would not need a new filing if the label were adjusted to reflect single use-only status, although a change of a device from prescription-only use to OTC use would require a new filing.

Software 510(k) guidance: patches okay

The provisions of the software 510(k) changes final guidance largely reflect those seen in the general 510(k) changes document, including references to ISO 14971 and the role of validation/verification in evaluating whether a new filing is needed. However, this document, too, makes a considerable concession, in this case on a major point in the realm of cybersecurity.

The draft guidance for software 510(k) changes addressed both stand-alone software devices and embedded device software, but that document had stipulated that patches and bug fixes would constitute a significant change and hence trigger a need for a new regulatory filing. (See *BioWorld MedTech*, Aug. 8, 2016.)

See FDA, page 9

Top 10

Continued from page 3

drive down LDL levels, to benefit patients with cardiovascular disease. And given the rate of coronary disease deaths – more than 400,000 are reported in the U.S. each year – the impact could be huge.

5. Long distance house calls

The rapid rise of mobile technology has made the futuristic-sounding notion of telehealth a near-term reality. But it's not exactly an effort that happened overnight, noted Jonathan Schaffer, of the Orthopaedic & Rheumatologic Institute. "The video phone [was introduced] at the 1965 World's Fair," he said. After all that time, the "technology is finally here and is being applied to health care."

Being able to reach patients at their homes via telecommunications devices has long been a goal. But 2018 is the year it's expected to happen. "Innovation succeeds where there's utilization," Shaffer said. Utilization requires engagement and engagement requires awareness and the necessary technologies. Now that those components are coming together, "we have a mandate to remove the geographical barriers to care."

Removing those barriers is expected to result in timelier, more efficient and more optimal outcomes as well as significant cost savings. Telehealth also can enable care for both the physically challenged and those most vulnerable to infection.

Hospitals are getting ready for widespread adoption in 2018, and reports predict 7 million patient users in 2018.

6. Beyond the syringe

As an infectious disease clinician, Steve Gordon, chair of Infectious Disease, said he would much rather prevent than treat. But the current rate of vaccine development – costing roughly $200 million and taking several years – is less than optimal, as are the requirements for shipping and storing. Those deficiencies were brought into stark relief during the recent outbreaks of Ebola and Zika virus.

In 2018, that's expected to change, with upgrades to vaccine platforms to support the rapid development of new vaccines, as well as breaking ground on new mechanisms to get the vaccines to patients across the globe. One example of that is the use of freeze drying vaccines, allowing for shipping to more remote locations. Companies also are finding faster ways to develop flu vaccines using tobacco plants, insects and nanoparticles.

And administering the vaccines also is undergoing innovation. Oral, edible and mucosally delivered vaccines, intranasal vaccines and vaccine chips are all under development. In 2018, a Band-Aid-sized patch for the flu vaccine is expected to be on the market.

"So we're getting more things on the menu," Gordon said. Work goes beyond outbreaks such as Ebola, with plans for hepatitis B virus and human papillomavirus vaccines also in the works. "So the field is obviously extremely exciting."

7. An end to chemo?

For years, the standard approach for treating breast cancer has been hormone therapy, chemotherapy and radiation, but those treatments are often not effective enough, in addition to having the side effect of damaging healthy cells. But in 2018, clinicians are looking at targeted therapies to add to the breast cancer treatment arsenal, possibly even one day supplanting chemotherapy.

Several targeted treatments, such as PARP inhibitors for patients with specific mutations in BRCA1 or BRCA2, and CD K 4/6 inhibitors for ER-positive/HER-2-negative breast cancer are doing well in the clinic. Detailed results presented at the American Society of Clinical Oncology meeting in Chicago, for instance, highlighted Astrazeneca plc's PARP inhibitor, Lynparza (olaparib), which reduced the chance of progression of advanced, BRCA-related breast cancer by 42 percent, delaying progression by about three months, in the phase III OLYMPIAD trial.

Treatment of breast cancer, which is estimated to kill more than 40,000 women in the U.S. each year, will be able to tap into the cancer genetics work that has come to define treatment of other malignancies such as melanoma. "This particular innovation is really taking the molecular underpinning of a disease," said Pauline Funchain, of the Taussig Cancer Institute. Targeted therapy has the potential to improve outcomes while decreasing side effects.

And as the space moves forward, "we are actually looking at an end" to chemotherapy," Funchain said, though when pressed for a prediction, added, "I'm not enough of a betting person to put a timeline on it, though."

8. Walking the road to recovery

Patients having surgery should avoid eating beforehand and then stay in bed while recovering, using pain medicines as needed. That's been the routine for decades, with doctors and hospital staff operating on the belief that having patients up and walking early in the recovery process would results in complications and readmissions.

But 17 years ago, Conor Delaney, chair of the Digestive Disease & Surgery Institute, wrote a paper showing that allowing patients to eat earlier, to walk around following procedures and to dose with analgesics rather than opioids results in improved recovery rates. Now, the ERAS, or enhanced recovery after surgery, protocol could change the way patients recover post-surgery.

"It's taken a long time because people were worried readmission rates would increase," Delaney said. But over the years the data have accumulated. "So this is just the time it's really exploding."

The ERAS protocol encourages regular walking to reduce complication rates and speed surgery, which reduces the chances of blood clots, nausea, infection, muscle atrophy and hospital stays. Patients also receive a postoperative nutrition plan to speed recovery, and, perhaps most importantly given the current opioid crisis, physicians use multimodal analgesia to limit opioid use.

See Top 10, page 9

Top 10

Continued from page 8

In 2017, collaborations were formed between surgical societies and large health care systems to drive funding and education for hospitals looking to implement the protocols on a larger scale, and the protocol is expected to really take off next year.

9. Eye in the sky

More than 90 percent of the alarms that sound in hospitals are not actionable, said Daniel Cantillon, of the Heart & Vascular Institute Cardiac. Telemetry monitoring systems can offer important warning signs, but the constant noise emanating from those systems means staff often fall prey to "alarm fatigue," causing them to miss an important signal.

As a result, reports have indicated up to 44 percent of inpatient cardiac arrests are not detected. The answer? Centralized monitoring – a sort of "mission control" operation in which patients' blood pressure, heart rate, respiration and pulse oximetry (for starters) can be monitored from afar using equipment such as sensors and high-def cameras. Monitoring can filter out unimportant alarms while triggering on-site intervention when needed. Basically, Cantillon explained, "we found a way to hone the attention of our caregivers to those patients who are in need."

An added benefit is making the hospitals quieter. By having the "eye in the sky" operated from an "off-site bunker, we can reduce alarms, so [hospitals] are more quiet, restful places," he said.

10. A cool approach for chemo hair loss

Of all that comes with a cancer diagnosis and treatment, hair loss might not seem the most urgent. But for patients, the loss of hair is an added worry. "From a patient perspective, it's very meaningful not to lose their hair," said Alberto Montero, a breast cancer specialist at the Taussig Cancer Institute.

Scalp cooling – it works by reducing the temperature of the scalp a few degrees immediately prior to and after chemo – has been shown to be effective in preserving hair in women receiving treatment for early stage breast cancer. In May, the FDA approved the system. ♦

FDA

Continued from page 7

The final guidance, however, seems to eliminate that flashpoint between the agency and industry by stating that a proactive software security patch that has no effect on the device other than to bolster cybersecurity would not require a new filing. The introduction of encryption or tools for remote access likewise would not create any regulatory liabilities, again assuming no effect on overall device function.

Other changes to software that would be relieved of any regulatory mandates include modifications made to allow the software to meet system specifications, but the addition of a diagnostic parameter to an instrument such as an electroencephalogram most likely would force a new filing. ♦

Product briefs

Depuy Synthes, of Raynham, Mass., reported the launch of two solutions for minimally invasive spinal fusion surgery (MIS) designed to simplify the procedure for treating degenerative disc disease in the back. The Viper prime system combines multiple instruments into one pedicle screw inserter tool that reduces the number of instrument passes. The single-use Concorde clear MIS discectomy tool allows surgeons to complete the degenerated disc-clearing process faster on average and more efficiently compared to traditional discectomy tools while increasing the amount of disc material removed. These products are being showcased at the North American Spine Society meeting, Oct. 25-28.

GS Medical USA, an Irvine, Calif.-based provider of spinal implants, instrumentation and surgical solutions, reported the full launch of the Anyplus direct lateral interbody fusion system, after three months of an alpha launch period, and the anterior and posterior disc prep sets.

Insightec Ltd., of Tirat Carmel, Israel, received approval from the **FDA** to initiate a pivotal study of the Exablate Neuro for treating dyskinesia symptoms or motor fluctuations of advanced Parkinson's disease patients who have not responded to medication. Exablate Neuro uses focused ultrasound to target and ablate tissue deep in the brain with no surgical incisions. MR imaging guides the treatment planning and delivers thermal feedback for real-time monitoring. For Parkinson's disease, the lesion is made in a portion of the globus pallidus, which is known to be involved in the regulation of voluntary movement.

Nuvasive Inc., of San Diego, said it will highlight the company's latest spine technology at the North American Spine Society Annual Meeting. Featured products include the Xlif Crestline, Lateral Alif, Modulus Xlif, Tlx system, Lessray and porous PEEK technology. The company will also unveil its Advanced Materials Science portfolio.

Sunnyvale, Calif.-based **Relievant Medsystems Inc.**, developer of the Intracept procedure for the treatment of chronic low back pain, reported the enrollment of the first patient in the INTRACEPT study – a level I, prospective, randomized clinical trial comparing the Intracept procedure to conservative care for patients with chronic low back pain. The INTRACEPT study will enroll up to 150 patients at up to 20 centers across the U.S. The primary efficacy endpoint is the mean change from baseline to three months post-treatment in the Oswestry Disability Index (ODI). The INTRACEPT study is the second randomized controlled clinical trial sponsored by Relievant, following the successful results of the SMART (Surgical Multicenter Assessment of RF Ablation for the Treatment of vertebrogenic back pain) trial, which supported the company's FDA 510(k) clearance. The INTRACEPT study has similar patient inclusion and exclusion criteria and endpoints for safety and efficacy as the SMART trial, and will demonstrate the performance of the therapy compared to real-world conservative care, as well as generate additional Health Economic outcomes data to support the reimbursement approval process.

Product briefs

Resmed Inc., of San Diego, reported the European release of its Airfit N20 classic nasal mask for positive airway pressure treatment. The Airfit N20 classic features a new adaptive frame with forehead support and the same Infinityseal cushion as Airfit N20 for an optimal fit. According to the company, the new mask provides a stable mask seal and is ideal for a comfortable night's sleep. The Airfit N20 classic is available now in Austria, Belgium, Bulgaria, Denmark, Estonia, Finland, France, Germany, Greece, Italy, the Netherlands, Portugal, Romania, Russia, Spain, Sweden and Turkey.

RTI Surgical Inc., a surgical implant company based in Alachua, Fla., reported the commercial launch of Fortilink-C IBF system with Tetrafuse 3-D technology. It is a 3-D printed polymer-based, cervical interbody device that incorporates macro, micro and nano-rough features on the entire implant surface. The Fortilink-C device is designed to allow bony ingrowth on all implant surfaces while maintaining radiolucent and bone-like mechanical properties that surgeons expect.

Zimmer Biomet Holdings Inc., of Warsaw, Ind., reported the official launch of its Vitality+ and Vital spinal fixation systems in the U.S. at the 2017 North American Spine Society Annual Meeting. The comprehensive Vitality+ spinal fixation system consists of Vitality+ Power for simple, controlled pedicle preparation and pedicle screw insertion; Vitality+ PSO for optimal pedicle subtraction osteotomy and vertebral column resection procedures; and Vitality+ Hooks with an extensive array of additional fixation options. The Vital spinal fixation system offers a compact solution for degenerative thoracolumbar procedures with its convenient, intuitive and optimized two-kit pedicle screw instrument configuration.

Other news to note

Biotelemetry Inc., of Malvern, Pa., reported that Biotelemetry Research, their global imaging and cardiac core lab, and **Advanced MR Analytics AB**, a body composition analysis company, created an exclusive alliance to launch clinical trials in non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. The partnership is intended to advance imaging by allowing for scanning of larger areas rather than individual organs or regions. The body composition analysis service translates a six minute whole body MRI scan into precise, 3-D-volumetric fat and muscle measurements. Biotelemetry Research is able to provide clinical trial sponsors with high-value information about drug efficacy and mechanisms of action.

The eleventh circuit U.S. court of appeals upheld $27 million in judgments to four women who received **Boston Scientific Corp**.' transvaginal pelvic mesh device, Pinnacle pelvic floor kit, according to New York-based Bernstein Liebhard LLP. A consolidated trial in November 2014 found Boston Scientific failed to warn doctors and patients about the risks and the individuals were separately awarded between $6.5 million to nearly $6.8 million. A multidistrict litigation is in process in the U.S. district court, southern district of West Virginia, with about 26,700 cases against Boston Scientific, according to Bernstein. Additional suits involve pelvic mesh devices marketed by American Medical Systems, C.R. Bard Inc., Ethicon Inc. and Cook Medical Inc. in that district. Transvaginal mesh devices for prolapse repair were reclassified as class III medical devices in 2016.

Switzerland-based **Lonza Group** reports its MODA-EM version 3.3 software enables microbiology quality control laboratories to comply with new regulatory guidelines. The program provides data integrity, data visibility and data review, is searchable and offers improved analytics, reporting, and web-based dashboards for access from various devices.

Tandem Diabetes Care Inc., San Diego-based touchscreen insulin pumps maker, reported that any features approved by the FDA in 2018 for its t:slim X2 insulin pump will be available at no cost through the Tandem device updater. Tandem and Animas also have extended the joint welcome program through March 31, 2018, to match expiration of Dexcom's program and Tandem's Touch Simplicity Today pump access program. Animas reported the closure of its U.S. and Canadian insulin pump business earlier this month, as well as chosen partnership with Medtronic plc to transition customers. (See *BioWorld MedTech*, Oct. 6, 2017.)

Orthopedics Extra

Keeping you up to date on recent developments in orthopedics

By Holland Johnson, Executive Editor

Study shows how growth factor aids stem cells' ability to regenerate damaged teeth

In a new study published in *STEM CELLS Translational Medicine*, researchers used a type of platelet-derived growth factor called PDGF-BB that enhances cells' ability to regenerate dentin-pulp complex. Many in the medical community view stem cell therapy as a promising new strategy for repairing teeth once thought to be irreversibly damaged by tooth decay or dental injuries. The benefits of human dental pulp stem cells (hDPSCs), isolated from the living connective tissue in the tooth's center, on such damage have been well documented in studies. There have been some limitations on how much mineralized tissue can be formed when scaffolds with hDPSCs alone were implanted in nude mice. More importantly, the narrow root canal of a tooth limits tissue infiltration and the revascularization process, which also worked against the implanted hDPSCs. Researchers at Shanghai Jiao Tong University's School of Medicine have found what they believe is a way to overcome these limitations. They showed that when scaffolds containing engineered cells were implanted in mice for 12 weeks, the group of mice treated using scaffolds seeded with PDGF-BB cells, a well-known potent mitogenic, angiogenic, and chemoattractive agent that has been widely used in tissue regeneration, outperformed the other groups when it came to generating more dentin-like mineralized tissue that showed positive staining for the DSPP protein – similar to tooth dentin tissue – and was surrounded by highly vascularized, dental pulp-like connective tissue. The researchers said their data demonstrated that the PDGF-BB possesses a powerful function in prompting stem cell-based dentin-pulp tissue regeneration. The article is titled "The effects of PDGF-BB on human dental pulp stem cells mediated dentin-pulp complex regeneration."

On-and-off fasting helps fight obesity, study finds

Up to 16 weeks of intermittent fasting without otherwise having to count calories helps fight obesity and other metabolic disorders. Such fasting already shows benefits after only six weeks. This is according to a study by Kyoung-Han Kim and Yun Hye Kim in the journal *Cell Research*. Intermittent fasting in mice helped to kick-start the animals' metabolism and to burn fat by generating body heat. The research team was led by Hoon-Ki Sung of The Hospital for Sick Children in Ontario, Canada. The research team in this study wanted to better understand the reactions that interventions such as fasting trigger on a molecular level in the body. They exposed groups of mice to 16 weeks of intermittent fasting. The recurring regimen saw the animals being fed for two days, followed by one day without anything to eat. Their calorie intake was not adjusted otherwise. Four months later the mice in the fasting group weighed less than those in the control group who continued to eat the same volume of food. The lower body weight of the mice in the fasting group was not the only effect. The fasting regime helped lower fat build-up in the white fat by increasing the brown-like fat (involved in burning energy and producing body heat) of mice on the high fat diet. Their glucose and insulin systems also remained more stable. In a further experiment, similar benefits were already seen after only six weeks of intermittent fasting. Through an analysis into the underlying biology involved, the researchers found that such intermittent fasting tempers an immune reaction in fat cells. There are changes in certain gene pathways involved in the immune system and the body's reaction to inflammation. A type of white blood cell known to play a role in fighting inflammation is triggered. Known as anti-inflammatory macrophages, these cells stimulate the fat cells to burn stored fats or lipids by generating heat. This happens during periods of intermittent fasting because there is an increase in vascular growth factor (VEGF) that help form blood vessels and activate anti-inflammatory macrophage. The article, titled "Intermittent fasting promotes adipose thermogenesis and metabolic homeostasis via VEGF-mediated alternative activation of macrophage," was published in October 2017.

Sites Medical licenses its Osteosync Ti to Integrity for use in their Flarehawk implants

Columbia City, Ind.-based **Sites Medical** has entered into a licensing agreement with **Integrity Implants**, to incorporate its Osteosync Ti technology into Integrity's multidimensional expandable interbody devices. Osteosync Ti technology is a highly porous titanium scaffold designed to meet the needs of today's patients from both clinical and economic standpoints. Its high friction coefficient is designed to ensure high initial implant stability and its open pore geometry and micro-texturing facilitate bone ingrowth. Preclinical testing has demonstrated bone attachment strength nearly twice that of titanium plasma spray and approximately seven times that of PEEK material at the five-week follow up period, a performance differential that can impact clinical outcomes, especially in spinal fusion patients. Osteosync Ti technology has also been engineered to reduce the potential for abrasion during implant insertion and associated debris-related inflammation. "We are very excited to work with Sites Medical," said Wyatt Geist, president and CTO of Integrity Implants. "As the market begins to recognize the need for implants that promote better short- and long-term stability, the Sites Medical Osteosync Ti technology offers us an opportunity to provide proven bone ingrowth capability at cost-effective levels.

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Orthopedics Extra

Continued from previous page

Fziomed receives approval for new confirmatory study of Oxiplex

San Luis Obispo, Calif.-based Fziomed Inc. received approval from the FDA to conduct a small confirmatory study of Oxiplex in the U.S. Oxiplex is an absorbable, synthetic viscoelastic gel that is applied following partial discectomy, with the intent to reduce postoperative leg pain, back pain and neurologic symptoms. “We have been working with FDA for many years to bring this technology to the U.S.,” said John Krelle, president and CEO of Fziomed, “and we are confident that a new level of cooperation with FDA will finally enable patients in this country to experience the benefits of Oxiplex following the large number of lumbar surgeries performed here.” Multiple U.S. and OUS studies have already demonstrated the benefits of Oxiplex and this study will target patients with higher levels of back and leg pain who do not always experience the level of pain relief offered by surgery alone. The company is working with Musculoskeletal Clinical Regulatory Advisers (MCRA) as both regulatory advisor and CRO on this study, which will be posted on Clinicaltrials.gov when open for enrollment.

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