POLICY & REGULATION
Medicare agency comes on board with adding UDIs to claims forms, p. 6

COMMERCIAL
Zimmer makes robotics its sixth acquisition of 2016, p. 5

RESEARCH & DEVELOPMENT
June sees several late-stage trial starts, p. 14

Medtech Insight

Issue 2

medtech.pharmamedtechbi.com

Pharma Intelligence Informa

July 25, 2016

Photo credit: Lightspring/shutterstock.com

OBESITY 2016:

Minimally Invasive Bariatric Devices Gaining Steam

ANNE STAYLOR anne.staylor@informa.com

With over two-thirds of US adults, equivalent to more than 136 million people, defined as overweight or obese (BMI >25 kg/m^2), there is no end in sight for the obesity epidemic. Bariatric surgery remains the gold standard for treating patients with morbid obesity (BMI >40 kg/m^2), but this is costly, irreversible and only 1% to 2% of the eligible patient population are willing or able to undergo these procedures. In 2015 alone, roughly 19 million US adults qualified as morbidly obese, and yet surgeons only performed an estimated 196,000 bariatric surgeries, including laparoscopic sleeve gastrectomies, gastric bypass surgeries, and laparoscopic adjustable bands according to recent estimates by the American Society for Metabolic and Bariatric Surgery (ASMBS). (*See Figures 1 and 2.*)

Patients, providers and payers all agree there is a compelling need for safe and effective products and procedures that are less invasive, less costly and more easily reversible than bariatric surgery. Fortunately, device innovators could be tipping the scales in the right direction. In the last 18 months, four next-generation obesity devices have reached the US market and several more are on the horizon that will help fill the product void between more invasive bariatric surgery and conservative weight loss methods (diet, exercise and drugs).

In January 2015, **EnteroMedics Inc.** received US FDA premarketapproval for the *MAESTRO System,* an implantable pacemaker-like device that intermittently blocks the vagus nerve to modulate feelings of hunger and satiety – the first medical device approved for obesity in over a decade. Six months later, in July 2015, **ReShape Medical Inc.**'s *ReShape Integrated Dual Balloon* became the first intragastric balloon system to be approved by FDA, beating **Apollo Endosurgery Inc.**'s *Orbera Intragastric Balloon System* to market by only three weeks. And most recently, **Aspire Medical Inc.** got an FDA PMA in June this year for its *AspireAssistAspiration Therapy System* that allows patients to aspirate part of their stomach contents out after each meal (*see a more detailed discussion below*).

With more than 20 emerging technologies in development, a broad array of endoscopic procedures and devices could reach the market to treat obesity and its metabolic comorbidities in the coming years. Despite some high-profile setbacks (e.g., **Satiety Inc.**, **Leptos Biomedical**, **GI Dynamics Inc.**), companies taking aim at this space could reap big rewards and expand the

CONTINUED ON PAGE 19

Over 100 event types

Over 100 catalyst types

Over 5,000 products

Meddevicetracker
Pharma intelligence | informa

Double the Power

Meddevicetracker with Medtech Insight reports is a new interactive real-time source of in-depth medical technology market intelligence

Meddevicetracker brings you closer to the medtech market, helping you to:

- Identify upcoming device regulatory events/filings
- Search for medtech clinical trial starts and data
- Find historical and forecasted procedure volumes data
- Monitor drug delivery technologies and identify partnership opportunities
- Quantify the market size for devices or diseases
- Discover forecasted market share of devices by type
- Understand the device competitive landscape and identify unmet clinical needs

Request your free demo today:
please visit - **www.meddevicetracker.com**


cover


9

16

explore more:

exclusive online content

UK reprocessing path
http://bit.ly/29Tgsfk
The UK Medicines and Healthcare products Regulatory Agency has issued new guidelines that open the door to re-manufacturers of single-use devices (SUDs) by setting out the conditions under which the activity is allowed.

FDA diabetes adcomm
http://bit.ly/29zivFF
Look for coverage of a closely watched July 21-22 FDA advisory panel meeting addressing the prospect of continuous glucose monitoring to replace, rather than simply complement, finger-stick blood glucose testing and, separately, the first hemoglobin A1C test to seek a point-of-care indication to help diagnosis diabetes.

Earnings season
http://bit.ly/2abmPMJ
How did industry bellwethers fare in the last quarter?

Innovation ramp-up Down Under
http://bit.ly/2abmPMJ
Medtech Insight finds out more about South Australia's push to nurture home-grown innovation, particularly the development of commercially viable, high-tech medical devices.

DEVICE WEEK
http://bit.ly/2arGJSY
Our weekly podcast, where *Medtech Insight* journalists discuss topics they are covering that impact the device and diagnostics community.

medtech.pharmamedtechbi.com

inside:

Medtech insight

DAVID FILMORE @MEDTECHDAVID
david.filmore@informa.com

TINA TAN @MEDTECHTINATAN
tina.tan@informa.com

SHAWN M. SCHMITT @MEDTECHSHAWN
shawn.schmitt@informa.com

REED MILLER @MEDTECHREED
reed.miller@informa.com

AMANDA MAXWELL @MEDTECHAMANDA
amanda.maxwell@informa.com

SUE DARCEY @MEDTECHINSIGHT
sue.darcey@informa.com

DANNY AL-FARUQUE @ALFARUQUE
danny.al-faruque@informausa.com

ELIZABETH ORR @ELIZABETHJORR
elizabeth.orr@informa.com

ASHLEY YEO @ASHLEYPYEO
ashley.yeo@informa.com

MAUREEN KENNY @SCRIPREGMAUREEN
maureen.kenny@informa.com

NEENA BRIZMOHUN @SCRIPREGNEENA
neena.brizmohun@informa.com

VIBHA SHARMA @SCRIPREGVIBHA
vibha.sharma@informa.com

JANET HANIAK SENIOR DESIGNER

GAYLE REMBOLD FURBERT DESIGN SUPERVISOR

RICHARD FAINT HEAD OF MEDTECH
richard.faint@informa.com

PHIL JARVIS MANAGING DIRECTOR

Editorial office:
52 Vanderbilt Avenue, 11th Floor, New York, NY 10017
phone 240-221-4500, fax 240-221-2561

CUSTOMER CARE:
1-888-670-8900 OR 1-908-547-2200
FAX 646-666-9878
clientservices@pharmamedtechbi.com

▶ join the conversation

We are tweeting, chatting, liking and sharing the latest industry news and insights from our global team of editors and analysts — join us!

@Medtech_Insight

Zimmer Biomet Mirrors Medtronic's Robotics Move With Medtech SA

REED MILLER Reed.Miller@informa.com

Zimmer Biomet Holdings Inc. has signed a definitive agreement to acquire French robotics company **Medtech SA** for about $130m, the companies announced July 18.

The Medtech deal is Zimmer Biomet's fifth acquisition of 2016. (*Also see " MNA ANALYSIS: Cardio And Ortho Billion-Buck Deals Headline Otherwise Slow Month " - Medtech Insight, 7 Jul, 2016.*) It comes less than a month after Zimmer Biomet agreed to pay about $1bn for **LDR Holding Corp.**, specifically citing the potential for LDR's spine technologies to boost its spine division. (*Also see "Zimmer Biomet Buys LDR To Boost Spine Revenue Growth" - Medtech Insight, 7 Jun, 2016.*).

Zimmer Biomet is the leader in the large joint segment of the orthopedics device market with around a third of the market share, but only has 5% of the global spine device market – 7% including LDR – which it estimates is the largest musculoskeletal market, worth about $10bn annually. Zimmer Biomet's spine division currently markets hardware and biologics for spine surgery, but does not have a robotic system like Medtech's *ROSA Spine*.

ROSA Spine allows surgeons to plan minimally invasive vertebral fusion surgery and, during the procedure, the robot aids instrument navigation and implant positioning, while tracking and adjusting for any movements or changes of the patient or in the surgical field, according to Medtech.

The US FDA cleared ROSA Spine in January for spatial positioning and orientation of instrument holders or tool guides to be used by surgeons to guide standard neurosurgical instruments during spine surgery. It is specifically indicated for the placement of pedicle screws in lumbar vertebrae with a posterior approach. ROSA Spine earned a CE mark in 2014. ROSA was cleared by FDA for brain surgery in 2012.

At the time FDA cleared ROSA Spine, Medtech CEO Bertin Nahum told *Medtech Insight* that his Montpellier-based company already had a sales staff of 26 people in the US. He said he expected ROSA to rapidly take share in the spine-surgery market, beginning with pedicle screw procedures, "by proving that, through our technology, any hospital, any surgeons, can successfully perform an [minimally invasive surgery (MIS)] technique even if they weren't originally trained on MIS." Currently, less than 20% of pedicle screw procedures are performed with a minimally invasive procedure, so there is plenty of room for expansion in this market segment, he said.

Commenting on the deal in a July 18 note, Wells Fargo analyst Larry Biegelsen writes "This acquisition is another example, along with **Medtronic PLC**'s recent agreement with **Mazor Robotics Ltd.**, **Globus Medical Inc.**'s upcoming robot launch and **NuVasive Inc.**'s stated interest in robotics, of the spine industry's growing interest in robotics." (*Also see "Robotic-Assisted Surgery: Taking MIS By Storm" - Medtech Insight, 26 May, 2016.*)

> "Currently, less than 20% of pedicle screw procedures are performed with a minimally invasive procedure, so there is plenty of room for expansion in this market segment."
> – Bertin Nahum, Medtech SA CEO

But although this acquisition will raise the profile of ROSA, Zimmer Biomet will have to do a lot of work to get ROSA to compete with Mazor's more established *Renaissance Spine*, especially in the US market, Biegelsen predicts. (*Also see "Medtronic Bets On Future Mazor Robotics Spine Surgery Systems" - Medtech Insight, 19 May, 2016.*)

Medtech reported on July 12 that there are 82 ROSA systems installed in hospitals worldwide and over 3,500 procedures have been performed with the system. However, most of these procedures were brain surgeries; the company celebrated reaching the 100th ROSA Spine procedure in May, and all of those were completed by four the same four surgeons. By contrast, Biegelsen reports, Mazor has marketed spine-surgery robotics systems in the US since 2007 and has a US installed base of over 80. Mazor's spine-surgery technology has been used in over 17,000 cases globally with more than 300 surgeons currently using one of their robots.

Zimmer Biomet will likely discuss their plans for ROSA Spine during their second-quarter earnings call on July 28.

TERMS OF THE DEAL

Following unanimous agreement of both companies' boards, Zimmer Biomet acquired 1,406,151 Medtech shares at €50.00 per share, representing 58.77% of Medtech's outstanding shares from Bertin Nahum, Newfund and other stockholders in a private transaction. Zimmer Biomet also bought all outstanding convertible bonds at €50.03 per convertible bond and warrants previously issued by Medtech to Ally Bridge Group at €17.17 per warrant. In accordance with French law, Zimmer Biomet will create a wholly owned subsidiary in France to to acquire the remaining outstanding shares of Medtech for €50.00 per share, in cash.

Zimmer Biomet plans to continue operations of Medtech at its current Montpellier headquarters, and retain Nahum as the leader of its robotic development activities.

Published online 07/19/2016

Medicare Agency Comes On Board With Adding UDIs To Claims Forms

DAVID FILMORE david.filmore@informa.com

The Center for Medicare and Medicaid Services is finally putting its support behind giving Unique Device Identifiers a place on insurance claims forms. In a letter dated July 13, CMS Acting Administrator Andy Slavitt joined US FDA Commissioner Robert Califf in urging adoption of UDIs for implantable devices on claims forms.

The letter is addressed to the Accredited Standards Committee X12, which has been working to adopt standards that would allow UDIs to be incorporated into health claims for several years. (*Also see "Efforts Accelerate To Add Unique Device IDs To Insurance Claims" - Medtech Insight, 10 Apr, 2014.*) The previous absence of CMS support for the move has delayed the efforts. The agency cited the significant cost and complications of revising hospital and payer computer systems nationwide as a reason to move cautiously.

The letter from Slavitt and Califf signals a shift. It requests that ASC X12 revisit its effort to capture the device identifier (DI) portion of the UDI on claims forms. "FDA and CMS are hopeful that ASC X12 can complete its work on the next version of the claims form ... for the relevant transaction standards to permit DI for implantable devices to be included in the claims forms," the letter states.

FDA has mandated that UDIs accompany class III devices since 2014. But for the codes to be leveraged for the purposes FDA envisions, in particular to support safety surveillance, facilitate recalls and improve device data collection, UDIs need to be incorporated into the healthcare system. (*Also see "UDI Expands, Questions Roll In, And Debate Over System Adoption Continues" - Medtech Insight, 17 Dec, 2015.*) Primarily, that means they should be entered in patient's electronic health records and linked to insurance claims, safety advocates argue. (*Also see "Questions Remain On Incorporating UDIs Into Health Care System" - Medtech Insight, 27 Nov, 2013.*)

HHS has taken some steps toward making UDIs a more routine element of health records. (*Also see "HHS Pushes To Incorporate UDIs Into Electronic Health Records" - Medtech Insight, 25 Feb, 2014.*) But the effort to give device-identifiers a space on claims forms has slowed, in part due to CMS' concerns. The Medicare agency has been lobbied to support UDIs on claims by several members of Congress. (*Also see "Senators Debate Adding Unique Device IDs To Claims Forms" - Medtech Insight, 10 Mar, 2016.*)

The letter from Slavitt and Califf highlight four over-arching reasons that they say UDIs should be captured by claims forms. The first two align with uses championed by FDA, but the latter two points highlight the advantages of UDI for providers and payers, including Medicare:

1. Allow for evaluation of product performance and identification of safety concerns for devices at the model level;
2. Facilitate the collection and analysis of patient data for devices at the model level that would be helpful in surveillance efforts and device innovations;
3. Help providers and certain payers to calculate and compare total costs and outcomes based on the device model used; and
4. Support program integrity by providing better information to link the patient and the implanted device to help track rebates from manufacturers back to the payer or provider.

Even with CMS' support, it could still be some time until UDIs actually show up on claims forms. The ASC X12 committee is expected to release the next updated standards by December of this year, but there will still be more work needed to change the forms.

Slavitt and Califf say they recognize the significant workflow and system changes that payers and providers will need to make, and also point out that additional resources will be necessary for CMS to "modify numerous legacy computer systems" so they can accept the new identifier information for implantable devices.

"HHS is committed to working collaboratively with our colleague stakeholders on the ASC X12 and is committed to a process that collects the DI on claims on a timeline and in a manner that minimizes the impact on state Medicaid agencies, health plans, small physician practices and hospitals in rural areas," they write.

Andy Slavitt

"HHS ... is committed to a process that collects the DI on claims on a timeline and in a manner that minimizes the impact on state Medicaid agencies, health plans, small physician practices and hospitals in rural areas," Slavitt and Califf write.

Published online 07/18/2016

House Bill Would Subject Local Medicare Contractors To More Transparency

SUE DARCEY sue.darcey@informa.com

Medicare administrative contractors (MACs) would have to make their processes more transparent and provide evidence backing their local coverage determinations (LCDs) for medical services and technologies under a bill introduced in the US House by Rep. Lynn Jenkins, R-Kan., July 11.

The medical technology industry for years has pushed the Center for Medicare and Medicaid Services (CMS) to lean on MACs to be more open with device sponsors about how the local contractors make coverage decisions. For example, in early 2015, AdvaMed pushed the House Energy and Commerce Committee to include a section on increasing transparency in the LCD process in its 21st Century Cures bill. (*Also see "AdvaMed Innovation Agenda Aligns With Capitol Hill Objectives" - Medtech Insight, 16 Feb, 2015.*)

HR 5712, cosponsored by Reps. Ron Kind, D-Wisc., and Gregg Harper, R-Miss., would require open and public MAC meetings, and require MACs to disclose their rationale and evidence supporting an LCD.

Under the proposed measure, the "qualifying evidence" that a contractor could use to back up an LCD would include results from randomized clinical trials or other studies published in peer-reviewed medical literature or a general consensus of the applicable medical community about use of a technology – such as a recognized standard of practice.

Further, the legislation would require that a draft LCD, a notice of a public meeting to review the proposal, and a record of meeting minutes would have to be posted for public review.

The bill would also prohibit the local contractors from adopting an LCD from another jurisdiction without first conducting its own independent evaluation of the evidence.

Photo credit: raffaelemontillo/shutterstock.com

ADVAMED, PATHOLOGY GROUP PRAISE BILL

AdvaMed President and CEO Scott Whitaker commended Jenkins for introducing the bill, saying it would improve MAC transparency and accountability.

The US industry association noted that the local contractors have the authority to make significant decisions impacting technologies and procedures, but that the MAC decision-making process currently "does not provide meaningful opportunity for stakeholder input or appeals."

Similarly, the College of American Pathologists, a medical society that represents pathologists and the practice of laboratory medicine worldwide, endorsed the legislation. "The bill seeks to ensure Medicare LCDs are made by qualified health experts through a transparent process based on sound medical and scientific evidence supported by medicine."

CAP added that, from a pathologist's perspective, a faulty LCD "can replace physician judgment with arbitrary and unsubstantiated rules, potentially denying patients treatment from which they could benefit." The society added that HR 5712 could stop the use of LCDs as a backdoor to CMS national coverage determinations by "prohibit[ing] the CMS from appointing a single MAC, either expressly or in practice, from making determinations to be used on a nationwide basis in a given specialty."

> "The MAC decision-making process currently "does not provide meaningful opportunity for stakeholder input or appeals," says AdvaMed's Scott Whitaker.

The bill has been referred to the House Energy and Commerce Committee. With little time left in the current legislative session, it is not likely to progress in Congress this year, but is likely to be reintroduced in the next session of Congress that will begin in January.

Published online 07/18/2016

21 Notified Bodies Declare Intention To Stay In EU Game

AMANDA MAXWELL amanda.maxwell@informa.com

A group of 21 European notified bodies have made public their intention to upgrade their activities and seek designation under the requirements of the future Medical Devices and IVD Regulations, which are likely to be adopted late 2016/early 2017.

This will be good news for those companies already working with the named notified bodies, as it will provide more certainty that they can move forward with the notified bodies for work under the new regulations.

There has been much speculation as to which notified bodies would continue operations under the new regulations and some concerns that many of the organizations may cease operations, forcing manufacturers to look elsewhere among a limited number of remaining bodies.

The latest list has been published by TEAM-NB, the European association of notified bodies, and features its members only.

To be a member of TEAM-NB, each notified body has to comply with its Code of Conduct whose requirements, the association claims, go beyond the current EU Medical Devices Directive (MDD) and *In Vitro* Diagnostics Directive (IVDD), and are a big step toward complying with the new MDR/IVDR. As such, the association is confident that its members are unlikely to encounter any significant hurdles to being designated under the new regulations.

At present, there are slightly more notified bodies designated to test under the MDD and IVDD that are not members of TEAM-NB than are. Indeed, the total number is hovering around the 60 mark.

But it is expected that many of these organizations will consider it unviable to find the resources to upgrade to the new regulations and that they will cease operations by the time testing has to be done under the new regulations.

The scope of conformity assessment activities offered by notified bodies currently operating in the medical devices and IVD spaces can be found on the European Commission's Nando website.

FOUR UK NOTIFIED BODIES, AND ONE IRISH

UK and Irish notified bodies account for five of the 21 organizations that have applied to be designated under the MDR and four of the 11 under the IVDR. BSI and SGS, both with a UK base, claim they are two of the largest medical device notified bodies within the EU.

The listing of the five may indicate confidence that the UK's Brexit decision to leave the EU will not impact regulatory agreements and trade in medical devices and IVDs with the EU, and that the UK will be implementing the two regulations. Or at the very least, it may indicate that they are not planning any disruption to existing or future client CE certification until the negotiations to leave the EU are completed.

There has been much speculation as to which notified bodies would continue operations under the new regulations.

Everyone is speculating, however. Nothing is certain, Medtech Insight notes, as the country waits to see what trade agreements are now possible following its departure.

Some have suggested that the UK could join the European Economic Area through the European Free Trade Association, and benefit from single market trade that way – just as Norway, which also has a notified body listed by TEAM-NB, has done. Others speculate that the UK may reach some mutual recognition agreement with the EU, just as Switzerland has done.

Medtech Insight notes, however, that no Swiss notified bodies appear on the TEAM-NB list. Francoise Schlemmer, director of TEAM-NB, told Medtech Insight that there had been a Swiss candidate, but it was de-notified before passing the association's Code of Conduct audit.

Turkey has two notified bodies listed under the MDR – but this is under an agreement that has been reached because it is an EU candidate member.

Members of TEAM-NB listed in the following table have voiced their intention to submit an application to be designated against the new Medical Devices Regulation and the IVD Regulation. There are 21 notified bodies in total meaning that all TEAM-NB notified bodies intend to continue operating.

IVD SHORTAGE?

It is particularly noteworthy among the TEAM-NB members that are seeking designation under the new regulations that nearly twice as many are intending to operate under the MDR compared with the IVDR.

There has been a great deal of speculation about the number of notified bodies required under the IVDR and their capacity since the new requirements will see some 80%-90% of IVDs needing the involvement of a notified body compared with some 10-20% under the current IVD Directive. This will be a big change for manufacturers and notified bodies alike.

In total, a five-year transition period has been agreed for the IVD Regulation, giving manufacturers until early 2022 (if the regulation is adopted, published and takes effect by early 2017) to comply with the new requirements. This contrasts with a three-year period for products falling under the Medical Devices Regulation.

But there is speculation whether the five years will be enough if there is not sufficient notified body capacity. This is

something that is worth monitoring and a lot will depend on the size of the IVD operations at each notified body designated under the IVDR.

TIMELINES

Notified bodies can be designated and notified under the MDR before early 2020, when the MDR is expected to be fully applicable. They can be designated and notified under the IVDR before the application deadline of 2022.

It seems from the current text of the MDR and the IVDR that notified bodies will be able to audit manufacturers and issue certificates in accordance with the MDR once they have been designated.

The requirements of the MDR and IVDR regarding notified bodies will apply in the early part of the second half of 2017. This covers a wide range of activities related to the auditing, designation and supervision of notified bodies under the MDR.

COUNTRY	MDR	IVDR*
Germany	7	3
UK	4	3
Netherlands	1	1
Denmark	1	1
Turkey	2	0
France	1	1
Ireland	1	1
Czech Republic	1	1
Sweden	1	0
Slovenia	1	0
Norway	1	0
TOTAL	**21**	**11**

**All notified bodies applying under the IVDR are notified bodies that are also applying under the MDR*

It seems likely that calls for all notified bodies to be jointly designated under the new regulations are not practical as it will be important to get manufacturer audits underway as soon as possible, even if notified bodies feel that first come, first served approach will result in an unfair advantage to those designated earlier on.

Schlemmer indicated that TEAM-NB will be working to help put its members in a good position of preparedness so they "are able to pass" the designation audits by the designating authorities "without non-conformities."

Current notified body notifications under the MDD and the Active Implantable Medical Devices Directive will expire in early 2020. Those under the IVDD will expire in early 2022. These dates will apply as long as the new regulations are adopted and enter into force by early 2017.

Published online 07/13/2016

EU Process To Re-Designate Notified Bodies: Steps and Timelines

AMANDA MAXWELL amanda.maxwell@informa.com

The European Commission's Notified Bodies Oversight Group (NBOG) has issued a best-practice guide for authorities involved in designating and redesignating notified bodies, as well as for the joint assessment teams that are involved in auditing notified bodies.

The process involves not only the designating authority of the member state where the notified body is based, but also joint-assessment teams made up of specialists from several countries, which work with the designating authority and the Commission to ensure that each notified body meets the necessary requirements for designation or re-designation.

This new guide, 2016-1, applies in the context of the Medical Devices Directive (MDD) and the Active Implantable Medical Devices Directive (AIMDD), and it lays out how the involved organizations should conduct the (re-)designation and scope extension of notified bodies. Although the guidance does not directly apply to notified bodies operating under the *In Vitro* Diagnostics Directive, designating authorities will consider the outcome of the Medical Devices Directive/ Active Implantable Medical Devices Directive joint assessment when deciding on a notified body's fitness to operate under the IVDD.

A designation for a notified body lasts up to five years. Because the new Medical Devices Regulation – which covers the scope of products currently regulated under the MDD and AIMDD – is due to be adopted and take effect by early 2017, with full application in 2020, the

EU is likely approaching the end of granting new designations for notified bodies under the current directives. This means that the majority of assessments going forward under the device directives will be for re-designations.

Given that the EU is moving toward a new regulatory era, an updated guidance will need to be issued under the future MDR, Medtech Insight learned. The next version is unlikely to be available until late 2017 at the earliest so it can reflect further experience gained in the interim. Otherwise, the updated guideline is likely to be similar to the current guidance.

BASED ON SEVERAL YEARS' EXPERIENCE

The guide, 2016-1, expands on the process outlined in the Commission's Implementing Regulation (EU) No. 920/2013 on the designation and supervision of notified bodies and takes into account experience that the designating authorities have gained in carrying out joint assessments so far, Rainer Edelhäuser, chair of NBOG, told Medtech Insight.

The Commission's Implementing Regulation was published in September 2013 as part of the EU's approach to tightening standards for notified bodies in the wake of the PIP breast implants scandal that came to light several years earlier.

The guidance is also important for notified bodies because they need to know what will happen, what to do when, and what they can expect, Edelhäuser said.

He added that it has taken some considerable time to draft the guidance, with the pre-assessment and post-assessment sections having to be adjusted to best practice more than once, he added.

The guidance contains an annex of activities and times. The dates are purely illustrative, Edelhäuser said. But they make it clear that completion of the process takes more time than most might expect. Some of the steps that are needed are detailed in the sidebar box, "Notified Body Designations: Things To Remember." Even more details can be accessed in the guidance.

Published online 07/14/2016

Notified Body Designations: Things To Remember

- Supporting documentation needs to be sent by existing notified bodies to the designating authorities around 18 months prior to the expiry of its national designation and around six months in advance of the anticipated onsite assessment.
- If 18 months is not long enough to carry out the necessary tasks – including notified bodies rectifying all nonconformities – then a designation might expire, or the notified body will be de-designated.
- For notified bodies applying for an extension to their scope of designation, the overall time period may be much shorter.
- It will be the job of the European Commission's Directorate-General for Health and Food Safety, called "Sante F," to select two national expert assessors from all designating authorities best-suited on the basis of their experience and language capabilities to effectively participate in the onsite assessment of a notified body.
- A full designation or re-designation should normally take a minimum of four days onsite with up to five days if interpretation.
- If the language in which the onsite assessment is to be conducted is not English, Sante F will arrange for interpretation to be provided at its expense. Up to four interpreters may be required for each onsite assessment.
- The designating authority and joint assessment team have to agree on a list of files that they want to review, including notified body audit reports of manufacturers and records of its technical file reviews and design dossier examinations, as well as copies of source data on which these are based.
- The designating authority will ask the notified body to respond to any nonconformity with a corrective and preventive action (CAPA) plan containing a thorough root-cause analysis. The urgency for receiving such a CAPA plan depends on the seriousness of the nonconformity.
- If any nonconformity represents a serious health risk, the notified body has to take immediate action. For all other nonconformities, the CAPA plan shall be produced within a timeframe defined by the designating authority, e.g., within a maximum of two weeks for any major issues raised and within four weeks for minor nonconformities identified. If necessary, further onsite follow-up assessments might be conducted by the designating authority.
- The designating authority will submit its final report to Sante F, which will upload reports from the final joint assessment team and the designating authority into a Commission Joint Assessments workspace, where both reports will be available to all of the designating authorities in the EU, European Free Trade Association (EFTA) and European Economic Area (EEA).
- After the upload of both final reports into the Commission's joint assessments workspace, known as CIRCABC, the other designating authorities and the Commission services can address questions, raise concerns and request further information from the designating authority in question. A process, described at length in the guidance, can then unfold to challenge the findings.
- When no questions and comments arise, one month after the upload of both the reports into CIRCABC, the designating authority can then formally designate or re-designate the NB and post the outcome on the European Commission's Nando website.

High-Risk Companion Diagnostics Need IDEs Prior To Drug Trial, FDA Says

SUE DARCEY sue.darcey@informa.com

Photo credit: angellodeco/shutterstock.com

Before starting a clinical trial for a drug that will be paired with a companion *in vitro* diagnostic, sponsors must ensure that the diagnostic assay has undergone analytical validation and, if it's a high-risk IVD, has earned an investigational device exemption (IDE) approval, the US FDA says in a new draft guidance on co-development of drugs and diagnostics.

The agency issued a guidance on the submissions and approval process for companion IVDs, defined as tests "providing information essential for the safe and effective use of a corresponding therapeutic product," back in 2014. Since then, industry groups have been waiting for this follow-up document from FDA providing more recommendations on the development process for companion tests. (*Also see "Companion Diagnostics Guidance Finalized, But LDT Context Will Be Key" - Medtech Insight, 31 Jul, 2014.*)

"It is important to understand the critical analytical performance characteristics of early prototype tests" and analytical validation studies that evaluate critical performance parameters should be completed "in advance of using the test in a trial that is intended to provide the clinical evidence" supporting companion diagnostic claims, the draft guidance released July 14 recommends.

Analytical validation studies evaluate a test's accuracy, precision, analytical sensitivity and specificity, and its reproducibility, according to the agency.

GUIDANCE OVERVIEW

The guidance advises that, as a general principle, any companion diagnostic to a drug should be approved contemporaneously with the corresponding therapeutic. Included in the draft are general recommendations to support winning market authorizations for therapeutics and their corresponding IVDs; regulatory requirements sponsors should be aware of in developing companion products; considerations for planning and executing therapeutic clinical trials including investigations of IVD companion products; and administrative issues that can arise.

The draft guidance notes that "co-development … is critical to the advancement of precision medicine," and lays out four purposes for companion diagnostics. The diagnostics are used to identify patients likely to benefit from therapeutics; to identify patients likely to be at risk for adverse reactions from drugs; to monitor responses to treatment, for the purposes of adjusting it to fit the patient's needs, and to identify patients in the population for whom the therapeutic has been found to be safe and effective.

KNOW YOUR IVD'S RISK STATUS

Sponsors must determine if their investigational IVDs are considered to be "exempt," "non-exempt significant risk" or "non-exempt, non-significant risk" products, the draft guidance states. One example of an exempt investigational diagnostic, according to FDA, is a test that is not used as a diagnostic, unless it is confirmed by another medically established diagnostic product or procedure. Additionally, to be exempt, the test can't require invasive sampling that presents significant risk to the subject.

Significant-risk IVDs include those that present a potential serious risk to the health, safety or welfare of a subject because the diagnostic is used in determining, curing or mitigating a disease presenting a serious risk. For such tests, an incorrect test result could have serious repercussions. On the other hand, non-significant risk IVDs are those for which an incorrect test result does *not* pose a potential for serious risk to subjects in a trial.

FDA asks for an evaluation to be conducted when use of a significant-risk investigational IDE is planned. The evaluation should be "sufficiently analytically robust" and be conducted prior to using the IVD in a drug clinical trial.

The agency wants the diagnostic's IDE submission to include:

- A description of the IVD cutoff value, i.e., the clinical decision points, in instances when such values are essential for use of the IVD in the trial;
- A description of the pre-analytical studies on topics like specimen handling and storage, analytical studies, and any results from studies designed to demonstrate the reliability of the assay;
- A description of and result from other analytical studies that support evidence the IVD does not expose subjects to unreasonable harm; and
- The clinical trial protocol, either through direct submission or by reference to the appropriate investigational new drug application.

DRUG TRIAL DESIGNS

The draft guidance advises on how to design appropriate clinical trials for co-development. It recommends that trials be designed "to support the claims for both the therapeutic product and IVD com-

panion diagnostic" at the same time, and to ensure the IVD trial strategy lines up with the approval goals for the therapeutic product.

The guidance also says that the "population of the subjects enrolled in the clinical trial is crucial," and notes that early testing may show a therapeutic product is "beneficial in the test-positive subgroup and harmful in a test-negative subgroup," for example. Therapeutic product makers and IVD sponsors should work together closely to understand how the IVD's analytical performance affects subject selection.

FDA also warns that "sponsors should be aware that using exploratory testing that is not sufficiently analytically validated or validated with inappropriate analysis methods may produce spurious associations."

But if a clinical trial is properly designed to establish safety and effectiveness of a therapeutic product in a population based on measurement or detection of a biological marker, the results of that trial can also be used to establish the clinical validity of the IVD companion diagnostic.

Another consideration for clinical trial design is to try and identify a population expected to benefit – or, to avoid serious toxicities – from the therapeutic. For this reason, sponsors should "pay close attention to the range of analytes and [to] establishing appropriate assay cutoffs" to adequately define these populations, FDA writes.

The agency says it will allow the use of IVD bridging studies, but in this situation, "the IVD sponsor should demonstrate that the candidate IVD companion diagnostic has performance characteristics very similar to those of the test that was used in the trial." This can be demonstrated through a bridging study between the two tests, using the original clinical trial samples and a pre-specified statistical analysis plan, to show that results between the candidate companion Dx is very similar to those results with the clinical trial assay.

Sponsors must know the status of their investigational *in vitro* diagnostic, and if it is exempt, significant risk, or non-significant risk.

The ideal bridging study would be one when all samples tested with the trial test, are retested with the candidate IVD companion test, and valid test results are obtained, then used to assess comparative performance.

ACHIEVING CONTEMPORANEOUS MARKETING AUTHORIZATIONS

FDA in the draft said it intends "to make every effort to coordinate the review so that the therapeutic product and the companion diagnostic can receive marketing authorizations at the same time." But to achieve this, the agency wants sponsors to plan ahead to assure coordination of the two separate submissions.

For example, co-development sponsors should look very carefully at the differences in review timelines for different products. FDA notes that "review times may be shortened even further for a marketing application of a breakthrough therapy-designated product."

FDA is accepting written comments on the draft guidance until Oct. 13 that should include the docket number FDA-2016-16735.

Published online 07/15/2016

St. Jude Agrees To Pay $39m To Settle Shareholder Suit

ELIZABETH ORR elizabeth.orr@informa.com

St. Jude Medical Inc. has agreed to pay $39.25m to settle class-action suits filed by shareholders who say the company artificially raised its stock prices by concealing heart-lead safety concerns.

The settlement was announced in June 7 filings in Minnesota federal court, and still requires a judge's final approval. Once finalized, the settlement will put to rest claims that St. Jude artificially raised its stock price by failing to inform investors of US FDA concerns with the safety of the company's *Durata* leads.

Durata leads were the successor to *Riata* leads, which St. Jude recalled in 2011 because they sometimes failed after insulation protecting the lead rubbed away. FDA issued a report in November 2012 that questioned whether Durata leads had been tested enough to ensure they weren't prone to the same kind of wear-related adverse event. In 2013, the agency sent St. Jude a warning letter addressing safety practices at the company's Sylmar, Calif., lead manufacturing plant. (*Also see "St. Jude Warning Letter Adds More Pressure On Firm's Leads Division" - Medtech Insight, 21 Jan, 2013.*)

St. Jude replaced both Riata and Durata leads with the *Optisure* line in 2014. But a manufacturing issue led to the recall of a batch of Optisure leads in January 2016. (*Also see "Another St. Jude ICD Lead Recall, But Impact May Be Limited" - Medtech Insight, 25 Jan, 2016.*)

The company's stock price dropped by 12% after FDA's concerns about Durata safety became public in 2012. Investors filed the class-action suit alleging securities fraud in December of that year.

If St. Jude had not settled the case, it would have gone to trial in 2017. The settlement doesn't include an admission of liability. St. Jude did not respond to a request for comment by press time.

In April, **Abbott Laboratories Inc.** announced it was buying St. Jude for $25bn. (*Also see "The Rumors Were True: Abbott Buys St. Jude For $25b To Create Third Cardiovascular Giant " - Medtech Insight, 28 Apr, 2016.*)

Published online 07/14/2016

OstomyCure's TIES Titanium Ileostomy Device Launches In Europe

REED MILLER reed.miller@informa.com

OstomyCure AS is rolling out its *TIES* (Transcutaneous Implant Evacuation System) at select centers in Europe, following receipt of the CE mark for the titanium ileostomy implant in late June, the Oslo-based company told Medtech Insight.

"We have a plan to bring it to a limited number of well-respected clinics in European countries over the next year or so, to come up with more patients and [refine the surgical] technique and implant," OstomyCure Chief Financial Officer Henning Mork said in an interview. The first centers to use TIES will be in Norway, Sweden, and other major markets such as Germany or Norway, he said.

The CE mark was based on experience in five patients in Europe and a total of 35 patients have used the device so far. The company is also developing a plan to conduct a clinical trial of TIES in the US, either on its own or with a partner company, Mork said.

TIES is suitable for any ileostomy – a surgical opening in the lowest part of the small intestine – regardless of the cause of the ileostomy. The company says it may eventually create another version suitable for colostomies – a surgical opening in the large intestine. The ostomy market is worth up to $2bn annually, the company projects.

BIG POTENTIAL IMPROVEMENT FOR PATIENTS

TIES is a small titanium tube that is surgically implanted in the wall of the abdomen, where the intestine and soft tissue grow into it to become an extension of the intestine. It protrudes a few millimeters from the skin. The opening is sealed tightly with a lockable plastic lid that serves as a stopper. The patient can open to drain waste whenever necessary. The lid causes the small intestine to gradually form a reservoir inside the implant over time. The patient can regularly clean the lid with soap and water.

In conventional stoma surgery, the surgeon extends the intestine a few centimeters beyond the abdominal wall into a bag attached to the stomach. Patients often have social limitations caused by the skin irritations, infections, allergies created by the stoma as well as the stress and inconvenience of visiting the toilet frequently, according to OstomyCure. Some patients also struggle with parastomal hernias, leaks, smell and unwanted noise with the external bag. Stoma bag technology has not changed much over the last 30 years, so TIES represents a major leap forward, according to the company.

> "Without the 3D technology, I don't think we would have managed to manufacturer it at all," says OstomyCure CEO Henning Mork.

Gastrointestinal surgeons can implant TIES with a minimally invasive procedure similar to that of traditional stomas. Potential rare adverse events with the device, according to the company, include infection, entero-cutaneous fistulas, or rejection. But Mork said that the initial clinical experience with TIES shows no major safety issues related to the device, including infections. "We have to respect we have just a few patients so far and not [such a] long time with it but it feels very stable so far," he said.

3D PRINTING SOLVES MAJOR PROBLEMS

Mork said that when the company started sponsoring human trials of its technology at the University of Oslo, the major challenge was getting the implant to integrate into the surrounding tissue to create a tight seal.

"It didn't go very well, actually. So we had to explant those patients quite fast. At no point, was there any kind of safety problem with the implant, but from a functional point of view, it wasn't working," he said. "Then the company was in quite a low period, but … we came up with the third version of TIES, which is the current one, and we had new management, we got new money from our investors and we came up with 'TIES 3.'" The current design has a porous framework all over the implant to promote tissue integration.

Many of features of the current version of TIES are different than the original designs. But the most important change is that now the device is built layer-upon-layer via additive manufacturing, or 3D printing, using a laser melting a powdered titanium material.

The firm previously "had big problems on the manufacturing side, because our sub-suppliers made some mistakes, so we had a production time of … five or six months, when it should have been more like two months, ideally," Mork said. "Without the 3D technology, I don't think we would have managed to manufacturer it at all. And now we have a one-to-two-week, efficient manufacturing time, which is helpful, and at a cost that is, at maximum, one-third" of the price to make earlier versions. Clinical trials with the latest version began in Paris and Oslo about two and a half years ago, Mork said.

Published online 07/14/2016

STARTS & STOPS: Cardiovascular And Neurology See Several Late-Stage Trial Starts

TINA TAN tina.tan@informa.com

Among June's selection of trial initiations, as recorded by Informa's Meddevicetracker, are several late-stage clinical studies in the areas of cardiovascular and neurology. These include: **Johnson & Johnson**'s Phase II/III trials in of its *ThermoCool* ablation catheter for treat atrial fibrillation; **Boston Scientific**'s Japanese Phase III study of its *JetStream* atherectomy system for treating peripheral arterial disease; **Keystone Heart**'s pivotal US trial of its *TriGuard* embolic protection device for use during transcatheter aortic valve replacement procedures; and **NeuroMetrix**'s Phase III study, to be conducted in partnership with Scripps Translational Science Institute, of its noninvasive, wearable pain relief device *Quell*.

The table below details other highlights in June's medtech trial initiations and completions.

Published online 07/18/2016

Trial starts and stops – June 2016

DATE	COMPANY	PRODUCT NAME	TRIAL NAME	INDICATION
TRIALS INITIATED				
Jun 28	Medtronic plc (MDT)	RestoreSensor for Chronic Pain	SCRATCHY (EU)	Neurology (Pain)
COMMENTS: To evaluate pain management outcomes of therapy combining one month of conventional spinal cord stimulation *plus* one month of paresthesia-free high-density spinal cord stimulation with *RestoreSensor* in patients with failed back surgery syndrome. Expects to recruit 20 patients.				
Jun 28	Medtronic plc (MDT)	RestoreSensor for Chronic Pain	TACTIC (EU)	Neurology (Pain)
COMMENTS: To evaluate pain management outcomes of therapy with long-term paresthesia-free high-frequency spinal cord stimulation with RestoreSensor in patients with failed back surgery syndrome. Expects to recruit 10 patients.				
Jun 28	Johnson & Johnson (JNJ)	ThermoCool Diagnostic/Ablation Catheters for Atrial Fibrillation/Flutter	Phase II/III - PRECEPT (US)	Cardiovascular (Cardiac Rhythm Management)
COMMENTS: To evaluate the *ThermoCool Smarttouch SF* catheter for the treatment of symptomatic persistent AF compared to a predetermined performance goal (PRECEPT Study). Expects to enroll 367 patients.				
Jun 21	NeuroMetrix, Inc. (NURO)	Quell for Chronic Pain	Phase III - STSI Study (US)	Neurology (Pain)
COMMENTS: Study conducted with Scripps Translational Science Institute (STSI) to evaluate effectiveness of Quell wearable pain relief technology in patients with cancer-related pain. Expects to enroll 40 patients.				
Jun 21	AtriCure, Inc. (ATRC)	cryoICE cryoablation probes for Dysrhythmia (Arrhythmia)	FROST (US)	Cardiovascular (Cardiac Rhythm Management)
COMMENTS: To evaluate intraoperative cryoanalgesia therapy using cryoablation in conjunction with standard of care (SOC) pain management compared to SOC alone. Expects to enroll up to 100 patients.				
Jun 20	Boston Scientific Corporation (BSX)	Jetstream Atherectomy System for Peripheral Arterial Disease (PAD)	Phase III - J-SUPREME (Japan)	Cardiovascular (Peripheral Vascular Disease)
COMMENTS: To evaluate the safety and effectiveness of the Jetstream Atherectomy System for the treatment of Japanese patients with symptomatic occlusive atherosclerotic lesions in native superficial femoral artery (SFA) and/or proximal popliteal arteries (PPA) (J-SUPREME Study). Expected to enroll 60 patients.				
Jun 15	Keystone Heart Ltd.	TriGuard Cerebral Protection Device for Ischemic Stroke	IDE - REFLECT (US)	Neurology (Stroke)
COMMENTS: Pivotal US regulatory study of embolic deflection device to assess its ability to protect the brain from emboli during transcatheter aortic valve replacement (TAVR), minimizing the risk of cerebral damage. Expects to enroll 285 patients.				

DATE	COMPANY	PRODUCT NAME	TRIAL NAME	INDICATION
Jun 15	Respicardia, Inc.	remede System for Sleep Apnea	PAS - TREAT-CSA	Respiratory disorders
COMMENTS: Post market study to assess the impact of sleep apnea treatment with, or without the remedē implant, on the well-being of patients. Expects to enroll 500 patients.				
Jun 14	Smith & Nephew plc (SNN)	Emperion Modular Hip System for Cartilage and Joint Repair	HISTORIC (AU)	Orthopedics
COMMENTS: Retro-prospective study of total hip arthroplasty with the *Emperion* modular primary stem in Australian centers. Target enrollment is 156 patients.				
Jun 14	Edwards Lifesciences Corp. (EW)	Sapien 3 for Cardiac Valve Surgery	IDE - COMPASSION S3 (US)	Cardiovascular (Interventional Cardiology)
COMMENTS: To evaluate the hypothesis that valve dysfunction of the *Sapien 3* is within the performance goal of 25% in subjects with a dysfunctional right ventricular outflow tract (RVOT) conduit with a clinical indication for intervention is currently recruiting participants. The study expects to enroll 156 patients.				
TRIALS COMPLETED				
Jun 27	Avenu Medical, Inc.	Ellipsys Vascular Access System for End-Stage Renal Disease (ESRD)	Phase I/II - 01-0012-01 (Mexico)	Renal
COMMENTS: To evaluate safety and effectiveness of catheter system for percutaneous creation of an arteriovenous fistula for ESRD patients requiring dialysis access.				
Jun 23	Novartis AG (NVS)	Total IgE Assay for Allergy	Phase II - CDIGE0012201	Allergy
COMMENTS: To determine the accuracy in measurement of total immunoglobulin E using a test device in atopic subjects.				

Source: Meddevicetracker

Q2 Breathes A Little Life Into Medtech IPO Scene

TINA TAN tina.tan@informa.com

2016 proved to be a slow starter for medtech IPOs with only one company pulling off an initial public offering in the first quarter. However, the public markets looked more amenable in the second quarter, with six completed IPOs.

According to deals tracked by *Strategic Transactions*, four companies filed for IPOs between April and June, of which two successfully completed their offering – both hitting their targets – within this period. [See Table 1] New Zealand's **Volpara Health Technologies Ltd.**, which is commercializing its breast imaging and analytics platforms for the early detection of breast cancer, filed for an IPO on the Australian Stock Exchange in March and in May it raised Aus$10m, while UK-based **Oncimmune Ltd.**, had publicized its intention to float on London's Alternative Investment Market (AIM) in April and then raised £11m in gross proceeds a month later. (*Also see "Oncimmune Hits IPO Target" - Medtech Insight, 18 May, 2016.*)

Four other IPOs – all on US stock exchanges – went through in the second quarter. Two were filed in Q1, ophthalmology company **Clearside Biomedical Inc.** and radiotherapy specialist **Sensus Healthcare Inc.** (*Also see "Medtech IPO Environment Cools With Sluggish Q1" - Medtech Insight, 6 Apr, 2016.*). The other two, however, had been filed last year. **Pulse Biosciences Inc.**, which is developing a novel tissue treatment platform for use in various indications including cancer, had filed its IPO in Dec. 2015, and waited seven months to raise $20m on the NASDAQ. **PAVmed Inc.** bided its time for a whole year, having initially filed its S-1 form with the US Securities And Exchange Commission in April 2015 and finally completing its IPO on the Nasdaq in April this year. PAVmed, which has five ongoing medical device programs, also had to contend with a fraction of the funds it had intended to raised – just $5.3m from the $20m it was initially expecting last year.

But while the medtech IPO scene looked a little livelier from quarter to quarter, activity levels are far behind those seen in 2015. The second quarter of last year recorded 10 completed IPOs, of which an impressive eight had been filed within the same period. (*Also see " IPO ROUND-UP: Public appetite for medtech stocks on the up " - Medtech Insight, 10 Jul, 2015.*) Indeed, it was a bullish market in Q2 2015, where there were three up-sized IPOs (**Biocartis NV**, **PureTech Health** and **Glaukos Corp.**) – something which has yet to be seen this year.

Worth noting is that these upsized IPOs had been mainly in the European stock exchanges, such as Biocartis' on the Euronext and PureTech Health on the London Stock Exchange. And this year so far, among the three companies that managed to pull off their IPOs promptly within a month or two of registering their intent, two – Oncimmune and Volpara – did so on non-US stock exchanges.

That said, with the recent Brexit vote throwing the financial markets into turmoil, it remains to be seen whether predictions of a worsening in the financing environment would deal a big blow to medtech companies looking to try their luck in the public markets for the remainder of this year.

Published online 07/14/2016

TABLE 1

Medtech IPOs filed and/or complete, H1 2016

Shaded rows highlight companies that filed and completed their IPOs within Q2

COMPANY	TICKER	MARKET	SPECIALTY	DATE FILED	MAX TARGET OFFERING PRICE	DATE COMPLETED	AMOUNT RAISED
Senseonics Holdings, Inc.	SENS	NYSE	Blood glucose monitoring	Jan-16	$51.75m	Mar-16	$42.3m
Clearside Biomedical Inc.	CLSD	Nasdaq	Ophthalmic drugs delivered via proprietary suprachoroidal space microinjector	Jan-16	$57.5m	Jun-16	$46.9m
Tactile Systems Technology Inc.	TCMD	Nasdaq	At-home treatment of chronic venous insufficiency	Jan-16	$86.25m	Pending	Pending
Sensus Healthcare Inc.	SRTS	NYSE	Superficial radiotherapy systems for skin cancers	Feb-16	$24.4m	Jun-16	$12.65m
BioLight Life Sciences Ltd.	BOLT	Nasdaq	Ophthalmic drugs and devices	Feb-16	$11.8m	Pending	Pending
Oncimmune Ltd.	ONC.L	London AIM	In vitro cancer diagnostics	Apr-16	£11m	May-16	£11m
AC Immune SA	ACIU	Nasdaq	Radiopharmaceuticals and diagnostics for neurodegenerative disease	May-16	Undisclosed	Pending	Pending

COMPANY	TICKER	MARKET	SPECIALTY	DATE FILED	MAX TARGET OFFERING PRICE	DATE COMPLETED	AMOUNT RAISED
Volpara Health Technologies Ltd.	VHT	Australian Stock Exchange	Imaging and analytics system for diagnosing breast cancer	Mar-16	Aus$10m	Apr-16	Aus$10m
PAVmed Inc.	PAVMU	Nasdaq	Developing multiple medical devices in the areas of surgery, infusion pumps, renal denervation, among others.	Apr-15	$20m	Apr-16	$5.3m
Pulse Biosciences Inc.	PLSE	Nasdaq	Nano-Pulse Electro-Signaling tissue treatment platform for various indications including cancer and dermatology, among other things	Dec-15	$23m	May-16	$20m
OrthoPediatrics Corp.	KIDS	Nasdaq	Radiotherapy for skin cancer.	Jun-16	$75m	Pending	Pending

Source: Strategic Transactions

Details of the companies that filed and/or completed an IPO in Q2 2016 are below:

COMPANY	DETAILS	UNDERWRITERS
Oncimmune Ltd.	Cancer diagnostics firm Oncimmune Ltd. grossed £11m and netted £9.8m ($14.2m) through its initial public offering of 8.46 million shares at £1.30 on London's AIM. Oncimmune was spun out of the University of Nottingham in 2002. Oncimmune's *EarlyCDT* blood tests are based on the presence of autoantibodies that react with protein targets in a panel of seven tumor-associated antigens (CAGE, GBU4-5, HuD, MAGE A4, NY-ESO-1, p53, and SOX-2 proteins), and can detect cancer up to four years earlier than other methods such as chest x-ray or CT scan. Its flagship product, the EarlyCDT-Lung test, achieved proof-of-concept in 2005 and was test marketed from 2009-2012, before being launched in the US in 2012. IPO proceeds will go towards commercialization expansion, and will also support further research into EarlyCDT's potential as a diagnostic for additional cancers including liver and ovarian tumors. Since inception, Oncimmune had privately raised £33.1m prior to the IPO.	Zeus Capital Ltd
AC Immune SA	On the heels of closing a $43.5m Series E round, AC Immune SA (radiopharmaceuticals and diagnostics for neurodegenerative diseases) filed for an initial public offering on Nasdaq. The company plans to use the IPO proceeds to further develop its therapeutic and diagnostic neurodegenerative disease pipeline, which includes three vaccine, five therapeutic, and three diagnostic candidates. Its most advanced is crenezumab (an anti-abeta antibody) in Phase II/III for Alzheimer's disease prevention and treatment, partnered with Genentech under 2006 collaboration. Other AD candidates include ACI24, a Phase II an anti-abeta vaccine; Phase Ib tau-targeted vaccine ACI35 (licensed to Janssen last year); a preclinical anti-tau mAb, licensed to Genentech in 2012; and a preclinical tau-PET imaging agent under development with Piramel since 2014. Under an alliance signed with Biogen in April 2016, it's also developing brain imaging biomarkers for two protein targets--alpha-synuclein and TDP43, both implicated in neurodegenerative diseases, including Parkinson's. Since its 2003 inception, AC Immune has raised $127.5m.	Credit Suisse Group Jefferies & Co. Inc. Leerink Partners LLC
Volpara Health Technologies Ltd.	Breast imaging firm Volpara Health Technologies Ltd. (also known as Volpara Solutions Ltd.; formerly Matakina Technology) netted Aus$10m ($7.3m) through its initial public offering on the Australian Stock Exchange. The company sold 20 million shares at Aus$0.50. Volpara develops and sells breast imaging and analytics platforms for the early detection of breast cancer. Products include VolparaDensity, a breast density assessment system based on mammogram scan results; VolparaAnalytics, a reporting dashboard to collect indicators including patient population, mammography units, and operator performance; and VolparaDoseRt, which gives clinicians information on patient-specific x-ray dose and applied compression pressure based on breast composition. IPO proceeds will be used to strengthen Volpara's sales team, expand marketing in the US and Western Europe, launch new products, and support development and expansion of Big Data predictive healthcare analytics products.	Undisclosed

COMPANY	DETAILS	UNDERWRITERS
PAVmed Inc.	One year after originally filing, PAVmed Inc. closed its initial public offering on Nasdaq. The company grossed $5.3m through the sale of 1.06 units at $5; each unit consists of one common share and one warrant to buy a share at $5 (exercisable beginning October 28, 2016 and expiring January 29, 2022). PAVmed had planned to sell 1.2 million units. The company has five programs in development--the *PortIO* long-term implantable vascular access device; *Caldus* disposable tissue ablation devices, including renal denervation for hypertension; CarpX percutaneous device for carpal tunnel syndrome; NextCath self-anchoring short-term catheters; and NextFlo disposable infusion pumps.	Benchmark Co. LLC
Pulse Biosciences Inc.	Pulse Biosciences Inc. (pulsed electric field technology to treat cancer and skin conditions) netted $18.4m through its initial public offering of 5mm common shares at $4. The company was formed as Electroblate Inc. in May 2014, and in November of that year, made a series of "roll-up" acquisitions that provided the firm with the platforms it works with today. (It acquired ThelioPulse, a spin out of the Alfred E. Mann Institute of Biomedical Engineering at the University of Southern California (AMI-USC) that was created to develop and commercialize nanosecond pulse electric field technology for dermatology indications; BioElectroMed (health-related bioelectric devices); and NanoBlate, a BioElectroMed spin-out that had nanosecond pulse technology and related intellectual property.) As part of the acquisitions, Pulse also licensed key IP from Old Dominion University Research Foundation and Eastern Virginia Medical School, and amended a license agreement with AMI-USC. Pulse is now further developing the nano-pulse electro-signaling (NPES) technology, a platform that uses nanosecond pulsed electric fields to stimulate cell signaling and cell responses (secretion, apoptosis, and necrosis), with an initial focus on solid tumors and skin warts. The company says that NPES has significant advantages over traditional radiofrequency, microwave, and cryoablation techniques in that it is non-thermal and non-ionizing, and reduces the potential for damage to surrounding healthy tissue. It is incorporating the NPES technology into its PulseTx delivery device, for which it's pursuing 510(k) clearance for soft tissue ablation. Pulse raised $8mm through a Series A round that closed around the time of the acquisitions in 2014.	Feltl & Co. MDB Capital
OrthoPediatrics Corp.	OrthoPediatrics Corp. (orthopedic implants for children) filed for its IPO. It claims to be the only one exclusively focused on pediatric orthopedics. Ten-year-old OrthoPediatrics developed and has regulatory approval for 17 surgical systems with applications in trauma, long bone deformity and correction, scoliosis, and sports medicine. Products include cannulated screws, locking cannulated blade and proximal femur plates, flexible nailing systems, and spine systems. Brands include *PediLoc*, *PediFlex*, *PediNail*, and *PediFrag*. Under an agreement signed in March 2016, OrthoPediatrics exclusively commercializes SpineGuard's PediGuard probes to US pediatric institutions. The company will use the IPO proceeds to pay accumulated and unpaid dividends on its Series B preferred stock, repay the balance outstanding under the revolver with Squadron, invest in implants and instrument, fund R&D, and acquire or invest in complementary products, technologies, or businesses.	BTIG LLC Piper Jaffray & Co. Stifel Nicolaus & Co. Inc. William Blair & Co.
Clearside Biomedical Inc.	Ophthalmic-focused Clearside Biomedical Inc. netted $46.9m in its initial public offering of 7.2 million common shares priced at $7 each. The company planned to sell 4mm shares priced between $14-16. The company's late-stage candidates are administered via the SCS (suprachoroidal space) microinjector. Just days before filing to go public, Clearside announced positive top-line data from its Phase II clinical trial of CLS1001, a formulation of triamcinolone acetonide for treating macular edema associated with non-infectious uveitis. It's also working on CLS1003 for macular edema associated with retinal vein occlusion (Phase II) and CLS1002 for wet age-related macular degeneration (preclinical). Clearside is backed by investors including Aju IB Investment, Cormorant Asset Management, Perceptive Advisors, and Rock Springs Capital Management. Its most recent equity financing was a $20mm Series C round in December 2015.	Needham & Co. Inc. RBC Capital Markets Stifel Nicolaus & Co. Inc. Wedbush PacGrow Life Sciences
Sensus Healthcare Inc.	Sensus Healthcare Inc. (noninvasive skin cancer treatment) netted $11.8m through its initial public offering of 2.3 million common shares (including the overallotment) at $5.50. Investors also received three-year warrants to buy 2.3 million shares at $6.75. The company originally intended to sell 1.8 million shares at $10-12 when it first set a range in March, but then modified the S-1 filing to reflect a new range of 1.75 million shares at $6.25 a month before closing the offering. Sensus, formed in 2010, developed and sells the SRT100 photon x-ray low-energy superficial radiotherapy system. Offered as an alternative to surgical procedures and high-dose radiation, the 510(k) and CE-marked device treats non-melanoma skin cancers including basal cell and squamous cell carcinoma, and is also effective for keloids. Proceeds from the IPO will be used for continued commercial expansion as well as development activities on new and existing products. Sensus reported $10.3m in revenue for 2015 and $4.7m in cash on hand as of March 31, 2016.	Neidiger Tucker Bruner Inc. Northland Securities

Source: Strategic Transactions

CONTINUED FROM PAGE 1

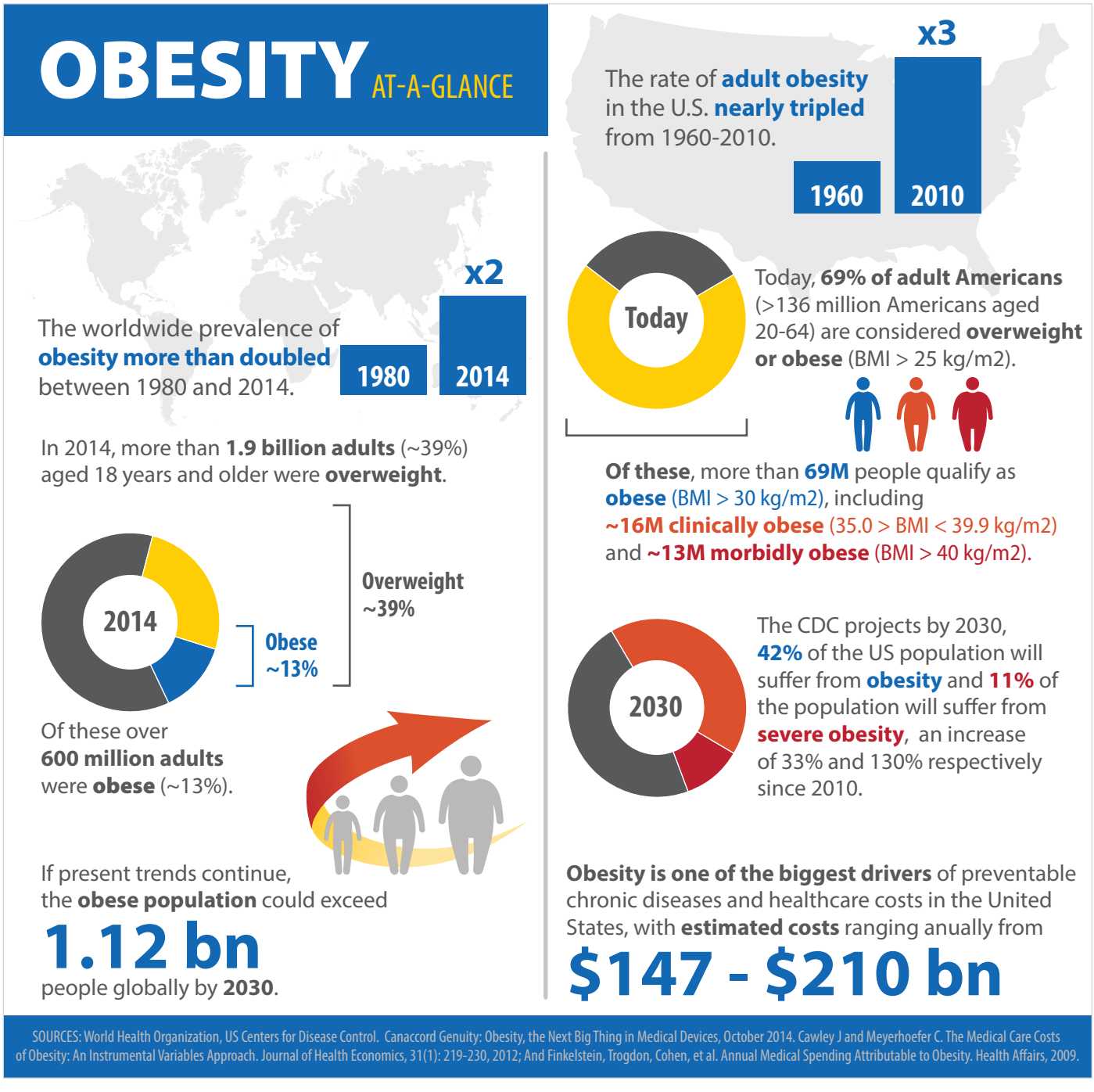
treatable population with minimally invasive solutions for morbidly obese patients as well as for patients with moderate and "cosmetic" obesity (BMIs of 25 to 40 kg/m^2) who are currently not candidates for bariatric surgery. These new, minimally invasive products and procedures, combined with improving reimbursement coverage and a favorable regulatory climate are driving growth in the US market for minimally invasive bariatric devices and instruments, which is projected to grow from $271.5m in 2015 to $525.1m by 2020, a CAGR of 14.1%, according to a *Medtech Insight* report. (*See Figure 3.*)

At the *Digestive Disease Week* (DDW) in San Diego in May, investigators presented promising research on several emerging procedures and devices, including endoscopic sleeve gastroplasty, dual path enteral diversion, aspiration therapy and swallowable intragastric balloons.

ENDOSCOPIC DUPLICATION OF BARIATRIC SURGERY

At DDW, researchers reported on several clinical trials that evaluated endoscopic approaches and technologies used to mimic more invasive bariatric procedures for primary weight control and for en-

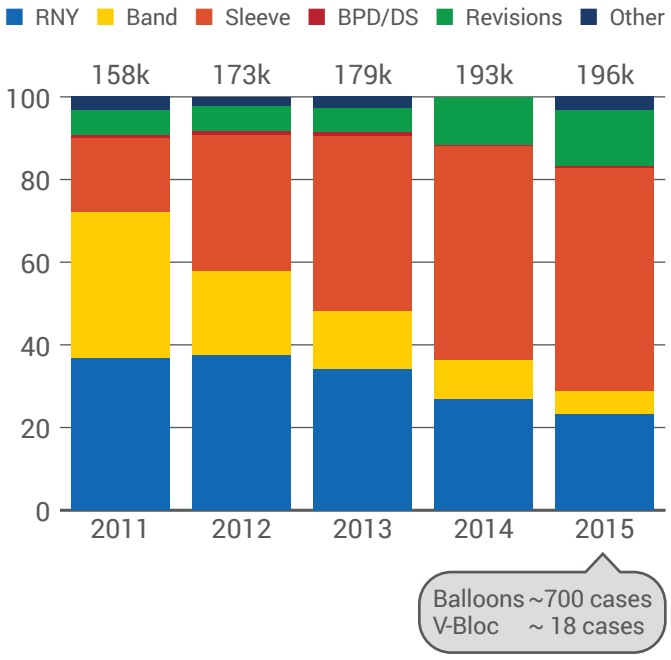
FIGURE 1



SOURCES: World Health Organization, US Centers for Disease Control. Canaccord Genuity: Obesity, the Next Big Thing in Medical Devices, October 2014. Cawley J and Meyerhoefer C. The Medical Care Costs of Obesity: An Instrumental Variables Approach. Journal of Health Economics, 31(1): 219-230, 2012; And Finkelstein, Trogdon, Cohen, et al. Annual Medical Spending Attributable to Obesity. Health Affairs, 2009.

FIGURE 2

ASMBS Bariatric Surgery Number Estimates, 2011–2015



SOURCE: American Society for Metabolic and Bariatric Surgery

doscopic revision of gastric bypass to address weight regain. While many of these approaches are showing promise in clinical trials, more research is needed to understand the physiological effects of these procedures and whether or not these approaches provide the same metabolic changes seen in more invasive bariatric surgeries that are the key to weight loss, improvement in metabolic markers, and resolution of T2D diabetes and other comorbidities. Moreover, because durability has been an issue with previous endoscopic solutions (e.g., **Satiety Inc.**'s *TOGA System*, **CR Bard Inc.**'s *EndoCinch*, etc.), physician adoption of these approaches will be highly dependent upon long-term efficacy data.

ENDOSCOPIC SLEEVE GASTROPLASTY

One emerging approach under investigation is endoscopic sleeve gastroplasty, a procedure that attempts to duplicate sleeve gastrectomy by endoscopically placing stitches, staples or plications along the greater curvature of the stomach to reduce it into the size of a narrow sleeve. At DDW, researchers presented the results of two different studies evaluating endoscopic sleeve gastroplasty using **Boston Scientific Corp.**'s *Articulating Circular Endoscopic (ACE)* Stapler and Apollo Endosurgery's *OverStitch Endoscopic Suturing System*.

Laurent Biertho, MD, of Laval University (Quebec City) presented two-year data from a Phase I, multicenter, non-randomized, prospective trial (n = 69/mean BMI range 30–47 kg/m^2) to evaluate the safety and efficacy of Boston Scientific's ACE Stapler for use in endoscopic sleeve gastroplasty. Researchers used the ACE Stapler to endoscopically create six to eight plications on the greater curvature, fundus and body of the stomach and two plications on the proximal antrum. The stapler head brings gastric tissue into a chamber using vacuum suction, where it creates a full-thickness plication using two circular rows of staples that are reinforced with a silastic ring. Overall, the data suggest the ACE procedure is safe and results in significant weight loss and quality-of-life improvement at 12 months and 24 months. Adverse events included mild to moderate pain, nausea and vomiting, which were seen in roughly 35% to 45% of patients. However, there were no serious adverse events (SAE) related to the device or procedure and no mortality. Mean excess weight loss (EWL) appeared to peak at 12 months (34.7%) and then decreased to 21% at 24 months. Of the 45 patients available for 24-month follow-up, 22 (49%) shifted to a lower obesity class, 20 (44%) remained in the same obesity class and 3 (7%) shifted to a higher obesity class. In Biertho's conclusions, he said a controlled trial with longer follow-up is needed to evaluate the durability of the procedure.

Reem Sharaiha, MD, of **Weill Cornell Medical College** (New York, NY) presented 18-month follow-up data from a retrospec-

FIGURE 3

US Obesity Devices Market, 2015–2020 ($m)

MARKET SEGMENT	2015	2016	2017	2018	2019	2020	CAGR (2015-2020)
Minimally Invasive/Laparoscopic Bariatric Surgical Instruments	196.7	206.2	218.7	232.8	246.5	261.7	5.9%
Laparoscopic Adjustable Gastric Banding Systems	66.4	62.4	63.7	67.8	74.9	85.6	5.2%
Intragastric Balloon Systems	6.6	11.9	17.0	23.0	30.5	39.5	43.0%
VBLOC Therapy Systems	1.8	4.6	11.8	22.5	48.8	96.0	121.5%
Other Emerging Devices	–	6.5	17.8	24.7	35.5	42.3	45.4%
Total	**271.5**	**291.6**	**329.0**	**370.8**	**436.2**	**525.1**	**14.1%**

SOURCE: Medtech Insight report #A153, "US Markets for Obesity Drugs & Devices," published February 2015

tive multicenter series evaluating 242 adult patients (BMI 30–40 kg/m^2) who had an endoscopic sleeve gastroplasty using Apollo Endosurgery's OverStitch. The OverStitch can be used to place full-thickness stitches using a running or interrupted pattern without removing the endoscope. At 12 months and 18 months, the mean total body weight loss was 12% and 19.8%, respectively, with a low incidence of complications (2% SAE rate). In terms of durability, Sharaiha said researchers did not routinely rescope patients to evaluate the integrity of the sutures at 12 or 18 months. However, in patients who were rescoped, there were a few broken sutures, but patients also formed bridging fibrosis because of the full-thickness nature of the sleeve.

GI WINDOW'S DUAL-PATH ENTERAL DIVERSION

Another promising bariatric procedure that uses endoscopically placed, self-assembling magnets is being developed by West Bridgewater, MA-based start-up **GI Windows Inc.** Six-month results from GI Windows' first-in-human study presented at DDW suggest endoscopic dual-path enteral diversion using the company's magnetic anastomosis device is safe and effective as a potential non-surgical bariatric treatment option for treating T2D in obese patients.

In the study, researchers from the Czech Republic used two standard flexible endoscopes and GI Window's *Incisionless Anastomosis System (IAS)* to create a jejunal-ileal side-by-side anastomosis (a connection between two segments of the bowel) in 10 patients that diverts a portion of ingested food from the proximal to distal small bowel. The procedure is designed to provide a less invasive approach to achieving long-lasting metabolic improvements in T2D that are comparable to that seen in patients who have bariatric surgery.

Here's how it works. Physicians advance a flexible endoscope into the upper jejunum and another one into the lower ileum, and then deploy magnetic devices from each endoscope into those segments of the small bowel. The devices emerge from the working channel of the endoscopes in a linear shape, but then "self-assemble" into an octagonal shape of almost 3 cm in diameter. Under trans-illumination and fluoroscopic guidance, the magnets are then aligned and coupled together, compressing the walls of the bowel in between. Over the course of seven to 14 days, the compressed tissue becomes necrotic, the outside tissue remodels and the coupled magnets are naturally expelled from the GI tract leaving behind a well-healed, compression anastomosis. (*See video of product on Medtech Insight's website*)

Patients who participated in the study included six males and four females between the ages of 22 and 58 years old, with a mean BMI of 41 (34.9–47.1 kg/m^2). Of these, four subjects had T2D and three were pre-diabetic. Patients were not given any dietary restrictions post procedure in order to evaluate the full-procedure effect. All patients had upper GI series at two weeks to examine flow through the anastomosis and to confirm expulsion of magnets. A follow-up endoscopy was conducted at two and six months to evaluate anastomosis patency.

WATCH

Visit our website to access the full article plus a video animation and a list of market players http://bit.ly/2904pzi

The dual-path enteral diversion was safely created in all patients and the IAS was expelled fully intact at a mean of 23 days without pain or obstruction. Two and six month endoscopies showed the anastomoses were widely patent and tissue was healthy with no evidence of ulceration. At six months, all patients experienced significant reductions in HbA1c and fasting glucose levels. For pre-diabetic patients, HbA1c levels were reduced from a mean baseline of 6.1% to 5.25%, and fasting blood glucose levels decreased from 119 mg/dl to 105 mg/dl. In patients with T2D, HbA1c levels decreased from a mean baseline of 7.8% to 6.0%, whereas fasting blood glucose levels decreased from 177 mg/dl to 111mg/dl. All patients had fasting glucose levels move from the diabetic or pre-diabetic range to the normal range at six months. The mean weight loss for all patients was roughly 28.4 pounds (13 kg), representing a 10.6% decrease in total weight loss.

Endoscopic dual-path enteral diversion is similar to the enteral bypass component of the biliary pancreatic diversion with duodenal switch (BPDDS) procedure, according to GI Windows CEO James Wright. However, it differs in that it also leaves the native channel open. "We think the dual path is an advantage because you're preserving the natural flow of the bowel and potentially limiting the nutritional deficiencies that are sometimes seen those types of procedures," Wright said in an interview with *Medtech Insight*. But he says it is the newly created path that provides the treatment effect that is similar to bariatric surgery. "By creating a new path for flow to go directly from the proximal to distal gut, a number of mechanisms occur that have been proven in bariatric surgery to impact type 2 diabetes," Wright explains. "You have dramatic rises in GLP1, which is a hind gut hormone which speaks to the pancreas and improves insulin production. So there's a very strong hormonal mechanism for type 2 diabetes, and there's also a modest but sustained weight loss, which is also what this patient group needs."

Because the magnets can be delivered through the working channel of an endoscope, Wright says it opens up a whole new set of possibilities for how these therapies can be implemented without surgery. (Study investigators created the anastomosis endoscopically with laparoscopic confirmation and assistance, if needed, for safety and to ensure correct placement of the magnets; however, they said this will be a completely endoscopic procedure.) The company plans to present 12-month data in an upcoming publication and to use the data to submit for a CE mark in Europe in 2017. The firm has raised $4m to date, and is leveraging the results of this study to help raise another $12m to do further research in order to submit data to FDA to conduct a pivotal study.

ASPIREASSIST: GETTING PAST FIRST IMPRESSIONS

Aspire Medical Inc. has developed an unusual but promising minimally invasive device for obesity that could potentially disrupt the market if clinicians, payors and patients look past their first impressions of the device and focus on patient outcomes. The company received FDA PMA approval June 14 for its AspireAssist Aspiration Therapy System, a novel minimally invasive bariatric device that allows patients to aspirate out a portion of their stomach contents after each meal through a tube attached to a port at the skin's surface.

Physicians insert AspireAssist's A-tube into the stomach just like a PEG tube (percutaneous endoscopic gastrostomy), which is

a 15-minute, outpatient procedure commonly performed in patients who are unable to eat or swallow. However, instead of using the tube to feed patients, the AspireAssist device is used to remove food from the stomach, thus reducing ingested calories and leading to weight loss. The A-tube is endoscopically inserted into the stomach, then threaded out through an incision in the abdomen, where it is capped with a skin port valve. The device requires that patients chew their food extensively to fit through the 6-mm tube, which means patients must eat slowly, and thoughtfully. Twenty minutes after eating, the patient attaches a handheld device to the skin port, flushes water from the attached reservoir into the stomach and then drains roughly 30% of the contents of his or her stomach into the toilet. Because the opening of the tube resides at the fundus (top of the stomach), about 70% of the food stays in the stomach. In general, patients do not feel hungry after aspirating, because the delay between eating and aspirating as well as the slower eating, gives the brain sufficient time to recognize satiety.

After the tube is placed, patients receive exercise and nutritional counseling and are monitored regularly for weight loss progress, stoma site heath, and metabolic and electrolyte balance. The physician-designed device also has a counter attached to it, which allows patients to use it 115 times before a new counter can be issued by the physician. This allows clinicians to monitor device usage and to ensure patients will return for follow-up (the device shuts off after 115 uses).

When combined with a diet and activity program, people can lose a substantial amount of weight, according to the company's pivotal trial results. At DDW, Christopher Thompson, MD, presented one-year data from the PATHWAY study, a US multicenter, randomized, controlled pivotal trial of 171 subjects with BMIs between 35 and 55 kg/m^2 randomized (2:1) to receive AspireAssist plus lifestyle therapy (n = 111) or lifestyle therapy alone (n = 60). Patients must have failed previous weight loss attempts and were excluded if they had previous abdominal or bariatric surgery, serious psychiatric disorders and eating disorders, among other criteria. All patients received medical monitoring for a year (14 visits), attended 4 group meetings and completed a baseline eating behavior assessment, which was reassessed at 14 (for the AspireAssist group), 28 and 52 weeks.

After one year, patients using AspireAssist lost an average of 12.1% of their total body weight compared with 3.6% for the control patients. The study also met both its primary endpoints: at 52 weeks, the mean percent EWL was greater than 10% (over the control) and at least 50% of the AspireAssist group achieved 25% EWL or more. The serious adverse event (SAE) rate was 3.6% (five SAEs in four subjects), including perioperative pain that resolved with pain medication after an overnight stay, mild peritonitis that resolved with IV antibiotics, mild ulceration that resolved with A-tube removal and A-tube fungal growth that resolved with A-tube replacement. In terms of eating behavior and patient satisfaction, subjects in the Aspire Therapy group showed high patient satisfaction and no evidence of binge-eating, worsening eating behaviors or excessive aspirating. One patient in the control group developed binge-eating syndrome at 28 weeks.

Surprisingly, the observed weight loss in Aspire Therapy subjects was greater than can be explained through aspiration alone. "The weight loss is much more profound than just removing calories so we think several things are going on," Thompson told *Medtech Insight*. "Patient surveys have found that patients chew far more than they did before, they eat slower, snack less and tend to eat less. So you're retraining how they eat. Additionally, when patients empty the reservoir into their stomach and fill it with water before draining it out, it causes their stomach to stretch further, which may cause them to feel full longer. There also may be something metabolic going on that we don't understand."

Thompson says the procedure is safe and reversible, which is a big plus for patients reluctant to have bariatric surgery. "If you look at bariatric surgery studies, that data generally looks at safety in the perioperative and immediate postoperative periods," he explains. "They are typically not looking at 10-year complication rates. You see many people coming back later with ulcers, strictures and other problems. It's an expensive procedure. Plus in the rare cases that they have a leak or more serious complications, it can be devastating. You create bariatric 'cripples.' So it's very relevant because of its safety, it's reversible, and it trains people to eat better."

Moreover, unlike bariatric surgery, Thompson says it changes people's relationship with food. Because patients must chew slowly and thoroughly, it helps protect against binge eating. It also mandates that people keep coming back (or it will shut off), and forces patients to come in for assessment of device use, diet specifics, weight trends, and nutritional counseling. This is not always the case with traditional bariatric surgery. Once patients have surgery, he explains, they can disappear and then come back with weight regain or other issues because they never really learned how to eat differently.

Whereas most endoscopic bariatric devices are approved for short-term use in patients with BMIs of 30 to 40 kg/m^2, the Aspire device seems to work in a wider range of weights. The FDA approved AspireAssist with a much broader indication for long-term treatment in patients (>22 years old) with moderate to severe obesity (BMIs 35–55 kg/m^2) who have failed to achieve and maintain weight loss through non-surgical weight-loss therapy. (The company is currently evaluating the device in Europe for patients with much higher BMIs.)

Not surprisingly, the device has been somewhat controversial as the concept of pumping food out of the stomach soon after eating to achieve weight loss almost seems like medically sanctioned bulimia. Although Thompson acknowledges the mechanism can be a mental hurdle that some people have to get over, he says the bottom line is that it works. "If you look at the graphs for other endoscopic procedures, there's a rapid weight loss, but then it starts coming back on and then it plateaus. With the Aspire, patients were still losing weight when we stopped the trial. They still haven't plateaued yet. As long as they keep using the device, it's going to work," he says.

Aspire Medical's CEO Kathy Crothall told *Medtech Insight* that most patients don't have a problem with Aspire Therapy as they've not succeeded with conventional means and don't want surgery. "When we first started talking about this widely, we had people shake their head in disbelief, saying it's gross, and we're irresponsibly encouraging uncontrolled eating," she said. "But at a recent training course on

bariatric endoscopy, there was no discussion of grossness. Over half the docs in attendance said they wanted to do this procedure. We think gastroenterologists will want to do this more than bariatric surgeons, as they are more comfortable inserting PEG tubes, although many bariatric surgeons are also trained in PEG tube insertion."

To date, around 500 patients worldwide have been treated with the AspireAssist, which was CE marked in late 2012. Crothall says of the 25 patients initially implanted with the device in Sweden in 2012, 12 are still using it today. The company is currently selling through distributors in Europe, and has been focused on gathering sufficient data to obtain clinical acceptance and ultimately reimbursement. Compared with bariatric surgery, which costs anywhere from $25,000 to $30,000 (not including complications), Crothall estimates the cost of Aspire therapy ranges from $8,000 to $13,000 over one year, including placement of the device, follow-up, lifestyle management and replacement of the expendable components of the external device. After one year, there is much less medical management as patients are used to using the device and have lost a large part of their weight. If patients want to have the device removed, physicians tell them to first taper off usage of the device to see if they can maintain their weight loss. If they can maintain their weight for a period of time without using it, Crothall says they can have it removed. However, obesity is a chronic disease and while some people will be able to make changes in their lifestyle and get off the device, she says it is unrealistic to expect that all patients will be able to do that. Furthermore, many patients will continue to use the device for many years, even if they are using the device only sporadically, with the device becoming, in effect, a "security blanket" in the event they fall off the wagon.

GASTRIC BALLOONS GAINING GROUND

Gastric balloons are emerging as another minimally invasive alternative to diet, drugs and bariatric surgery for patients with mild to moderate obesity (BMI 27–40 kg/m^2). Also called intragastric balloons, these temporary space-occupying devices are designed to reduce the size of the stomach and induce a feeling of satiety that leads to reduced food intake and weight loss. Although Apollo Endosurgery's Orbera Intragastric Balloon System and ReShape Medical's Reshape Integrated Dual Balloon System were the first to reach the US market, several next-generation intragastric balloons and space-occupying devices are in development that could receive regulatory approval in the next several years.

A NOVEL PROCEDURE-LESS GASTRIC BALLOON

Traditionally, gastric balloons require endoscopic insertion and removal, but Natick, MA-based Allurion Technologies has developed a unique, "procedure-less" gastric balloon device that can be swallowed in a doctor's office without the use of endoscopy or anesthesia and is naturally excreted about four months later. (*See Figure 4.*)

At DDW in May, Ram Chuttani, MD, director of interventional gastroenterology and endoscopy at **Beth Israel Deaconess Medical Center** and an assistant professor of medicine at **Harvard Medical School**, presented four- and six-month results of a small multicenter study evaluating the safety of Allurion's Elipse Gastric Balloon and its effect on metabolic parameters, quality of life and weight loss. The Elipse is 85% thinner than silicone balloons, and flexible enough to fold into a swallowable capsule and pass through the GI tract. Patients swallow the encapsulated balloon, along with a thin delivery catheter for filling, and stomach placement is confirmed with X-ray. Once the capsule enters the stomach, it degrades and the physician fills the Elipse with 550 ml of fluid. After filling is complete, the catheter is detached, the fill valve seals shut and the catheter is removed from the mouth. The valve was designed to weaken over time and open at about four months, allowing the balloon to empty and pass through the GI tract.

FIGURE 4

Elipse Gastric Balloon

Weight was measured every two weeks, and metabolic parameters were assessed at baseline and at trial exit. The Impact of Weight on Quality of Life-Lite (IWQOL-Lite) questionnaire was administered at baseline and trial exit to measure the effects of weight loss on Physical Function (PF), Self-Esteem (SE), Sexual Life (SL), Public Distress (PD), Work (W) and Overall (O).

Of the 34 patients enrolled in the study, there were 23 females and 11 males, with an average age of 42 years and a mean BMI of 34.8 kg/m^2. All 34 devices were swallowed without endoscopy or sedation and all catheters successfully detached. One patient aborted the procedure prior to filling the balloon, whereas two patients withdrew due to symptoms at one day and at eight weeks. Of the 31 patients remaining, six received an experimental balloon design which self-emptied and was passed as intended. In the remaining 25 patients, the balloon also self-emptied and passed as designed. Of these, one emptied earlier (at 12 weeks) and passed naturally, but the data were carried forward. Of the 24 remaining, all self-emptied at four months, and passed naturally, although four were excreted via vomiting. There were no serious adverse events, but researchers reported adverse events that are commonly seen with gastric balloons during the first 48 hours, including abdominal pain (25%), nausea (53.6%) and vomiting (64.3%). All adverse events were either self-limiting or resolved with medication.

At four months, the mean weight loss was 10 kg, percent total body weight loss was 10%, and percent excess weight loss was

39% (100% of the weight lost was from fat). All balloons were safely excreted and mean waist circumference and HbA1c were reduced by 8.4 cm and –0.16%, respectively. Improvements were also seen in triglycerides (–16.4 mg/dl) and LDL (–9.7mg/dl), and quality-of-life scores. At six months from placement, 92% of the weight lost was maintained. Researchers said the overall weight loss at four and six months was similar to that seen in prior studies of Apollo Endosurgery's Orbera Intragastric Balloon System, which received FDA PMA in August 2015.

Because the Elipse does not require endoscopic placement and removal, Allurion's CEO Jonathan Wecker told *Medtech Insight* that the device will make the procedure more attractive to both patients and physicians. "We looked at the market for gastric balloons and said, 'Why isn't this already a billion dollar business?'" said Wecker. "We concluded that the cost and inconvenience associated with the two endoscopic procedures have held it back. By taking two endoscopies out of the equation, we can decrease patient risk and save a lot of money for the system and patients [up to $2,000 for each endoscopy]. It also saves time, and allows physicians to care for more patients and focus on building a really great medical weight loss program around the balloon. The cost savings can be allocated to the program, whether it is nurses, nutritionists, dieticians or exercise physiologists, which we think adds a lot of value for patients." Although the company has yet to determine a price point for the device, Wecker estimates that Elipse could be 30% to 50% less than the intragastric balloons that are currently on the US market, which cost anywhere from $7,500 to $8,500 depending on the length of the behavioral program.

The device could potentially be placed by any trained medical professional, but Wecker notes that it's important to have a physician trained in gastrointestinal endoscopy in the network and available in the event of potential complications. He says it is too early to look at those specifics, but acknowledges that it could expand patient access if internists and other primary care physicians could prescribe the device.

Founded in 2009 by Shantanu Gaur and Samuel Levy, who were students at Harvard Medical School at the time, the Natick, MA-based company spent several years refining the design before obtaining CE mark in December 2015. Since then, the device has been in a limited commercial release in Europe (primarily France and Italy, with some patients in the UK) using a combination of direct sales people and distributors, according to Wecker, who adds that Allurion has started selling Elipse in the Middle East following its first launch in Kuwait this summer. In terms of bringing the device to the US market, Wecker says the company is actively involved in discussions with FDA to finalize a protocol for US approval, and hopes to start implanting patients in a pivotal trial in 2017. If all goes well, Wecker says the Elipse could reach the US market as early as 2019.

SWALLOWABLE, GAS-FILLED GASTRIC BALLOONS

San Diego, CA-based Obalon Therapeutics has also developed what could well be the next intragastric balloon to reach the US market. The company has completed a pivotal trial and submitted a PMA to FDA for the Obalon Balloon System, a swallowable gastric balloon (or series of balloons) that is filled with gas, placed without sedation and removed endoscopically at six months.

At DDW, Shelby Sullivan, MD, director of bariatric endoscopy at **Washington University School of Medicine** in St. Louis, presented the results of the SMART trial (Six-Month Adjunctive Weight Reduction Therapy), a double-blind, randomized, sham controlled multicenter trial evaluating the safety and efficacy of the Obalon Balloon. Researchers at 15 study sites in the US randomly assigned 387 enrollees to either the treatment group or a control group. Individuals in the treatment group were asked to swallow three capsules (one at 0, 3 and 12 weeks) which each contained an Obalon balloon. Immediately after participants swallowed the capsules, the balloons each were filled with 250 cc of a nitrogen-based gas via a small catheter attached to the capsule. For the control group, researchers asked these individuals to swallow three sugar-filled capsules (also once every three weeks). The researchers then mimicked the process of filling the sugar capsule with gas so that participants in this group did not know that they were in the control arm of the study.

Sullivan reported that within the Obalon Balloon treatment group, the average loss of total body weight was 6.81%, whereas the control group's average weight loss was 3.59% at six months. Investigators also found that 64.3% of subjects who received the Obalon Balloon achieved at least a 5% total body weight loss, compared with only 32% of the control group ($p<0.0001$). Individuals in the treatment group also experienced improvements in their systolic blood pressure (p-value 0.002), fasting glucose (p-value 0.0007), LDL cholesterol (p-value 0.0416) and triglycerides (p-value 0.0046).

Reported adverse device events include mild or moderate abdominal pain (73.7%), nausea (54.5%), indigestion/heartburn (12.7%), vomiting (14.6%), bloating (13.1%), burping/belching (10.1%) and diarrhea (6.6%). There was one serious adverse device event (bleeding gastric ulcer) in a subject on high-dose non-steroidal anti-inflammatory drugs (prohibited in protocol) after orthopedic surgery.

According to Obalon chief financial officer William Plovanic, the Obalon Balloon's swallowable and incremental delivery method, use of gas, and side-effect profile are what differentiates it from other balloons in the market. All intragastric balloons require the use of anti-emetics and anti-spasmodics to minimize nausea and abdominal pain. But the side effects with the Obalon balloons are much more mild and tolerable than with other balloons, according to Plovanic. He says that Obalon's balloons are more tolerable because they are smaller (250 cc) and gas-filled, which means the balloons are lighter than other balloons and rise to the top of the stomach, which allows them to be delivered over time.

The company CE marked in 2012 its first-generation balloon (which was approved for three-month use) and has sold more than 25,000 Obalon balloons internationally in the European Union, Mexico and the Middle East. The Obalon Balloon is used in conjunction with a diet and behavior modification program and is indicated for temporary use for patients with a BMI of 27 kg/m^2 or greater (OUS) who have previously failed a supervised weight control program.