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Intragastric Balloons And Other Innovations To Inflate Weight-Loss Devices Market

MARION WEBB marion.webb@informa.com

The highly competitive global market for minimally invasive weight-loss (bariatric) devices is predicted to rise from $137m in 2016 to $290m by 2021, a CAGR of 16%.

This is driven in large part by the rising obesity epidemic worldwide, which affects more than 600 million people worldwide. According to the World Health Organization, 65% of the world's population live in countries where being overweight and obese kills more people than being underweight. Adding to the epidemic is the growing number of people – one in every 10 – who are obese and have Type 2 diabetes.

With the vast majority of people remaining undertreated, there is ample room for companies to tap into this potentially multi-million dollar global market.

A number of smaller, innovative companies have developed next-generation technologies, in particular in the area of intragastric balloons, that are either in clinical trials or expected to hit the market in the near future. This, in turn, will spell competition in a market that has been widely dominated by a few key players.

According to *Meddevicetracker*'s "Minimally Invasive Weight Loss Devices Market" report, the minimally invasive bariatric devices market is divided into three segments: laparoscopic adjustable gastric banding (LAGB), intragastric balloons and implantable neuroregulators and gastric stimulators *(Also see "Obesity 2016: Minimally Invasive Bariatric Devices Gaining Steam" - Medtech Insight, 20 Jul, 2016.)* (See Figure 1).

LAGB -- which involves placing an inflatable silicone band around the upper portion of the stomach to restrict the stomach's capacity – accounted for 53% of total global sales in 2016. This segment, however, has seen a major decline in recent years due to significant safety and efficacy issues and that trend is expected to continue with global sales falling from $72.3m in 2016 to $24.7m by 2021.

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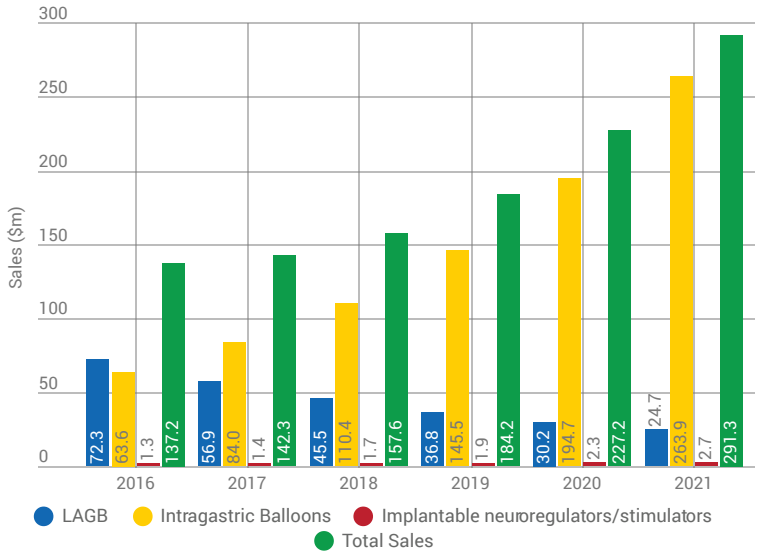
FIGURE 1

Minimally Invasive Weight-Loss Devices Market Forecast, By Segment ($m), 2016-2021



Source: "Minimally Invasive Weight Loss Devices Market," Meddevicetracker

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

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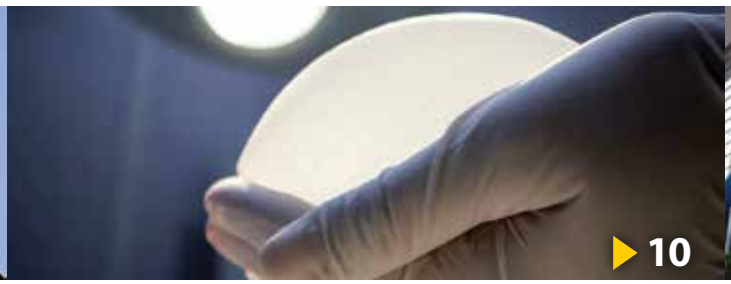

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Medtech insight

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
MARION WEBB @MEDTECHMARION
marion.webb@informa.com
SUE DARCEY @MEDTECH_INSIGHT
sue.darcey@informa.com
FERDOUS AL-FARUQUE @MEDTECH_DANNY
danny.al-faruque@informausa.com
ELIZABETH ORR @ELIZABETHJORR
elizabeth.orr@informa.com
CATHERINE LONGWORTH @MEDTECHCATE
catherine.longworth@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@pharma.informa.com

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VC DEALS ANALYSIS:

Only Way Is Up As October Puts 2017 Ahead

TINA TAN tina.tan@informa.com

The venture financing climate in 2017 has proven to be more favorable than in 2016, after October's total takings of $295.1m pushed the year's total deal value to date to $5.28bn, surpassing 2016's $5.14bn and even the $5.23bn recorded in 2015. And with two more months to go before the year is out, the gap will be widening even more, although by how much remains to be seen.

October saw 29 deals that raised $1m and over, as recorded by Medtech Insight's VC financing deal tracker. This is veering more toward the higher end of deal volume seen across the different months this year so far, which had July recording a whopping 35 deals and June 33. Nonetheless, October's deal volume beat September's 25 transactions and was twice as many as the paltry 14 recorded in October last year.

Of the 29 deals, 26 disclosed financial details and more than two-thirds of this group were small investments of $10m or under. (See Figure 1.)

This explains some of the disparity between the large deal volume and relatively modest deal value for October. Looking across the last five years, however, it seems that the deal value falls not too far from the levels seen in October last year ($240m) and in October 2013 ($296m). (See Figure 2.) The Octobers in 2014 and 2015 had each benefitted from one exceptionally large round, which skewed the total deal value. In 2015, there was a $115m round from consumer-focused genetic testing company 23andMe while 2014 saw a huge $542m round from MagicLeap, the visual display technology specialist started up by the co-founder of Mako Surgical Rony Abovitz.

CLOSED-LOOP NEUROMODULATION SEALS BIGGEST DEAL

The paucity of big-buck deals is evident in the month's list of top five fundrais-

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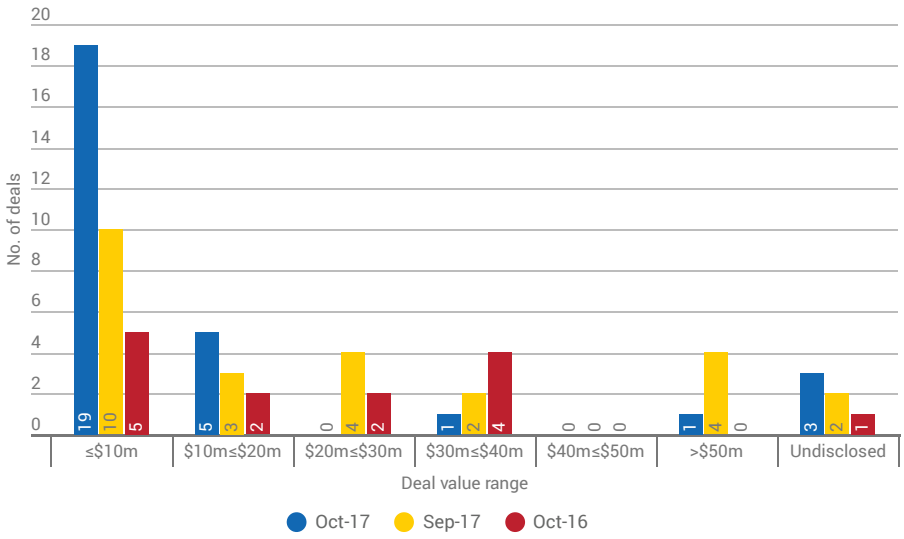
FIGURE 1

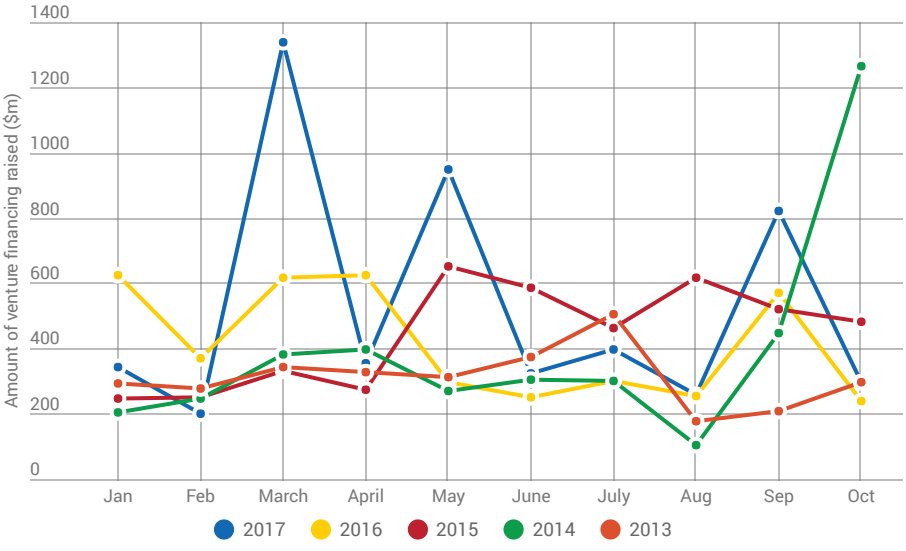
No. Of Deals By Amount Raised, Oct 2017 Vs Sept 2017 Vs Oct 2016



Source: Medtech Insight VC deal tracker

FIGURE 2

5-Year Trend: Monthly VC Deal Value, Jan-Oct 2013-2017



Source: Medtech Insight VC deal tracker

New UK Pathway To Cut Access Times For Breakthrough Products By Up To Four Years

IAN SCHOFIELD ian.schofield@informa.com

Health minister Lord O'Shaughnessy said the new arrangements would "guarantee future collaboration between the life sciences sector and the NHS post-Brexit."

Photo credit: Arno Mikkor

The UK government has backed the creation of an "accelerated access pathway" (AAP) under which a handful of selected breakthrough innovations – medical devices, diagnostics, drugs and digital products – could reach patients up to four years earlier than under standard assessment procedures.

The new pathway, to be introduced in April 2018, is expected to shorten the overall time to market for certain "transformative" new products, mainly by allowing cost-effectiveness evaluations to be carried out in tandem with the regulatory approval process. It will also offer companies early price negotiations and the potential for "flexible and confidential commercial arrangements."

Candidate products will be selected by a new "Accelerated Access Collaborative" chaired by former GlaxoSmithKline chief executive Sir Andrew Witty and comprising representatives of national regulatory and evaluation bodies, with input from industry, patients and clinicians. The AAC will be set up by the end of the year and the first products to enter the new pathway are expected to be identified from April 2018.

The government makes clear, though, that a commitment to faster access to what will no doubt be expensive new products must be balanced against the financial sustainability of the National Health Service. The new pathway, it says, must be "cost neutral" for the health service and "must deliver improved value to the taxpayer." To this end, a new strategic commercial unit will be established within NHS England to negotiate what the government calls "cost-effective deals."

The proposals are contained in the government's long-awaited response to the Accelerated Access Review (AAR), an independent report produced in October 2016 by Professor Sir John Bell and supported by the Wellcome Trust. In its response, the government broadly supports the proposals outlined in the AAR, which looked at ways of speeding up access to innovative new health technologies.

Health minister Lord O'Shaughnessy said the new arrangements would not only benefit patients but would "guarantee future collaboration between the life sciences sector and the NHS post-Brexit – benefiting the British economy and creating jobs."

Life science companies have been pushing for mechanisms to shorten times to market for innovative products and strengthen the life sciences sector, particularly as uncertainty mounts over the UK's relationship with the EU after Brexit in March 2019.

It's no surprise then that industry has broadly welcomed the announcement – albeit with some caveats about the need for high-level political leadership and NHS commitment to make the project succeed.

The Association of British Healthcare Industries welcomed the government's response, saying the move would "significantly speed up the time taken for patients to access lifesaving MedTech."

ABHI CEO Peter Ellingworth said the association was "pleased to see key MedTech recommendations reflected" in the response. "Delivering a consistent set of national, regional and local routes to market will support the diverse nature of the MedTech sector and help ensure that NHS patients have improved access to new technologies. Providing greater central alignment through the Accelerated Access Collaborative is an important step to speed innovations through the varied support programs."

Steve Bates, CEO of the BioIndustry Association, said the government's response to AAR was "a key piece in the jigsaw of UK government life science policy that will set the environment for our sector in the lead up to Brexit and beyond. It fits between the publication of the Life Sciences Industrial Strategy in the summer and ahead of both an anticipated Sector Deal and the outcome of the Treasury-led Patient Capital Review later in the year."

Bates pointed out, though, that "no strategy can succeed without a corresponding plan of action. Polling undertaken by the BIA earlier this year showed that 82% of NHS staff were unaware of either the Accelerated Access Review or the proceeding government strategy Innovation, Health and Wealth."

Moreover, he said, while the government refers to numerous other initiatives such as NHS Test Beds and the Innovation Scorecard, BIA polling "reveals that only 5% of NHS staff are aware of these two programmes. If the Review's ambition for innovation is to truly take hold then it requires both NHS buy-in and top-level government leadership."

On the academic research side, Professor Paul Workman, chief executive of the Institute of Cancer Research, welcomed the new pathway, noting that while the number of treatments

and technologies that secured a breakthrough designation "could be quite small," this was "a genuine opportunity" to accelerate access to real innovations.

THE ACCELERATED ACCESS PATHWAY

The core of the initiative is the new accelerated access pathway, which is intended to align and coordinate regulatory, reimbursement, evaluation and NHS diffusion processes for breakthrough innovations. "We will make the process from bench to bedside quicker, cheaper, and easier for innovators and the NHS," the government says.

Its aim is to "bring forward by up to four years patient access to these selected, highly beneficial and affordable, innovations." As well as drugs, devices, diagnostics and digital products, these could include "repurposed medicines where a new indication is found for an existing product."

> "Providing greater central alignment through the Accelerated Access Collaborative is an important step to speed innovations through the varied support programs" – ABHI CEO Peter Ellingworth

The government expects around five innovations a year to gain breakthrough designation and go onto the new pathway, but stresses the need to avoid any extra costs to the NHS. Any products placed on the AAP "that are cost additive will need to be offset by products that deliver cost savings, beyond those already factored into NHS plans," it says. "Efforts will be focused on those products that will deliver the greatest benefit to patients and improve value for money."

Each breakthrough product will benefit from "bespoke case management, which will coordinate across partners to streamline the journey," according to the government. "In return for these commercial benefits, we expect industry to come forward with a cost proposition that delivers additional value for patients and the NHS beyond that achieved under the current system, and is affordable."

To spur collaboration between companies and the NHS when negotiating commercial agreements, the government says that a new strategic commercial unit is to be established in NHS England to give it "enhanced commercial capability" by April 2018. There is "clear demand" from innovators for win-win commercial deals and the new function will be able to develop these types of arrangement.

In parallel, the commercial liaison team at NICE will support commercial engagement between companies and NHS England, "creating a smooth interface for companies throughout the appraisals process."

"TRANSFORMATIVE" DESIGNATION

The government in its response does not go into great detail about the criteria a product will have to meet to merit "transformative" (or breakthrough) designation, saying only that "a new transformative designation should be applied to those innovations with the potential for greatest impact."

The AAR itself defined such innovations as "the most strategically important products with the potential to deliver significant benefits in cost or outcomes," and suggested criteria such as significant improvement to patient-relevant outcomes, improved affordability, unmet need, strategic importance to the NHS, alignment with NHS priorities, and clear and measurable outcomes.

HORIZON SCANNING

An important component of the new scheme will be the early identification of what is coming through company pipelines. The new pathway will offer horizon scanning for new technologies to identify a subset of potential breakthrough products that could benefit from the AAP, the government says, adding that this will be a "key capability required for a forward-looking NHS that can articulate its priorities to industry, and prepare to deliver against those priorities."

It notes that the PharmaScan database currently enables horizon scanning for pharmaceutical products, and that NHS England is currently building on these capabilities to create a parallel system suitable for medical technologies. In addition, the recently established National Institute for Health Research Innovation Observatory is now using data analytics to "explore trends in health innovation across drugs, medical technologies, diagnostic tools and healthcare services."

ACCELERATED ACCESS COLLABORATIVE

The job of selecting candidates for the new pathway will fall to the new AAC, which will comprise representatives of the NIHR, NICE, the Medicines and Healthcare products Regulatory Agency (MHRA), NHS England, NHS Improvement and the government.

Input to the AAC will be sought from industry and patient groups that have "sufficient breadth of experience and independence to allow them to inform AAC discussions on the different technology types and conditions those technologies might benefit." Further details will be published on the membership of the AAC, which the government expects to be in place in late 2017.

The government stresses the importance of understanding and evaluating the impact of the new pathway over time. In line with the AAR's recommendation, it says, "we believe that the AAC should be responsible for measuring and evaluating the impact of our accelerated access programme and assessing the industry response to it. The views of the AAC will be informed by parties across the system, who will be represented in the group."

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Newman Out As CDRH Compliance Chief, Maisel In As Acting Director

SHAWN M. SCHMITT shawn.schmitt@informa.com

Photo credit: Ferdous Al-Faruque

Robin Newman (second from left) answers questions with top CDRH officials, including William Maisel (second from right), at The Medtech Conference in September.

Robin Newman is out as director of the Office of Compliance within US FDA's device center, leaving the post after only 18 months on the job. Agency stalwart and top scientist Bill Maisel has been named as acting head.

Newman left FDA on Oct. 20 to join **Johnson & Johnson**'s device unit as worldwide VP for clinical research and development, returning to the device industry from where she came. She was VP of quality management for Siemens Healthcare Diagnostics for more than five years when she was tapped for the compliance office role in February 2016.

Maisel, who is FDA's deputy center director for science, has been collecting "acting" titles of late. He took over as acting director of the Office of Device Evaluation in April following the departure of John Sheets from the agency. Sheets, who, like Newman, also worked in industry before joining FDA, left after 10 months as ODE head. *(Also see "Maisel Reassumes Acting FDA Device-Evaluation Chief Role As John Sheets Departs" -Medtech Insight , 31 May, 2017.)*

Maisel's ever-growing list of jobs at FDA appears to be in line with the agency's plan to build a new "super office" within the Center for Devices and Radiological Health that will essentially dissolve and replace the Office of Compliance, ODE, and the Office of Surveillance and Biometrics. *(Also see "'Super Office' To The Rescue: FDA's Device Center Is About To Undergo A 'Total Product Life Cycle' Makeover" - Medtech Insight, 29 Sep, 2017.)* Maisel will lead the new "Total Product Life Cycle" office, which will aim to bring pre- and post-market experts together to provide the agency with better visibility of products, device-makers and various device classes. The goal is to improve and streamline FDA's decision-making on issues impacting everything from early-stage product development to approval and post-approval compliance and surveillance, and back around to development of next-generation device iterations.

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Health Canada Throws MDSAP Lifeline To Small Device-Makers

SHAWN M. SCHMITT shawn.schmitt@informa.com

Small medical device manufacturers worried about meeting Health Canada's upcoming deadline to be audited to the Medical Device Single Audit Program have been thrown a lifeline by the agency, whose MDSAP Consortium has reduced the amount of time that auditors will spend at companies' facilities.

In an Oct. 31 notice, Health Canada said device-makers with 45 or fewer employees will see a 10% reduction in audit time, while those with 15 or fewer employees will see a 20% reduction. The agency made the change after receiving comments from Canadian companies concerned that they will not be MDSAP-compliant by Jan. 1, 2019. *(Also see "Manufacturers' Worries Grow Over Canada's MDSAP Deadline" - Medtech Insight, 12 Oct, 2016.)*

After that date, manufacturers won't be allowed to sell product in Canada if they have not undergone an MDSAP audit. MDSAP will replace Health Canada's Canadian Medical Devices Conformity Assessment System (CMDCAS).

"Manufacturers that cannot make the transition to MDSAP by Jan. 1, 2019, will be subject to compliance actions, including the potential for cancellation of medical device licenses," the agency wrote in its notice, strongly urging companies to contact auditing organizations to schedule an MDSAP audit as soon as possible.

"Auditing organizations may not be able to accommodate all requests for transition in late 2018," Health Canada warns.

The agency also announced other measures to help expedite the MDSAP process, including streamlining the audit approach by reducing the number of tasks that must be performed during an audit, and decreasing by 20% the audit time for all manufacturers that must undergo surveillance and recertification audits. Expectations were also clarified for surveillance audits, with the goal of cutting audit time.

"Other mechanisms to improve efficiency and reduce audit times are also being explored by the MDSAP Consortium and will be announced in the near future," Health Canada states.

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Repeated Quality Systems Issues Bring Philips Consent Decree

ELIZABETH ORR elizabeth.orr@informa.com

A newly finalized consent decree blocks **Philips Healthcare** from making or distributing automated external defibrillators (AEDs) until the company fixes manufacturing issues at Massachusetts and Washington state facilities.

The decree, which was formalized in a Massachusetts federal court by Judge Denise Casper on Oct. 30, follows eight years of repeated FDA concern over quality systems issues including Philips' failure to fully address complaints. The company, which is a division of Dutch firm **Royal Philips Electronics NV,** first announced that it had reached an agreement with the government on Oct. 11. *(Also see "Philips' Profit To Be Dented By FDA-Decreed AED Sales Halt" - Medtech Insight, 11 Oct, 2017.)* Under the terms of the consent decree, Philips and executives Carla Kriwet and Ojas Bush are barred from "manufacturing, processing, packing, holding or distributing" AEDs and similar units until the Andover, Mass., and Bothell, Wash., facilities comply with FDA regulations and meet other requirements.

Kriwet is business group leader for Philips' Patient Care and Monitoring Solutions (PCMS) business group, a division of which markets the company's AEDs, while Bush is the vice president over the PCMS quality and regulatory department.

The government laid out its case for the consent decree in an Oct. 11 complaint, which recounts a series of violations and concerns stretching back to 2009. Recently, a 2015 inspection of the Washington facility found that the company's corrective and preventive actions (CAPA) were inadequate following customer complaints of IRC R92 resistor failures during use of the *HeartStart HS1* and *FRx* defibrillators, even as Philips continued to receive similar complaints. In addition, the inspectors found that Philips didn't ensure purchased components met specifications and the company didn't validate its risk evaluation software.

FDA inspectors found similar issues at the Massachusetts facility later in 2015. For example, after reports of injuries acquired during use of the *Q-CPR* meter to assess chest compressions during CPR, Philips added a warning that recommended use of a chest pad, but took no further actions even after the company learned of more injuries. The company also didn't investigate a test failure while verifying a battery change, and violated design change validation rules by distributing the Q-CPR with instructions for use that contradicted those of the supplier with no documented attempt to reconcile the difference.

The violations found during the two 2015 inspections echoed those found during earlier inspections of the same facilities, the legal documents state. The Bothell plant had been inspected in 2012 and 2013, and an earlier Seattle plant was inspected in 2010. FDA inspectors at the time documented QS violations in areas including design controls, purchasing controls, process controls, CAPA and complaint handling. Similarly, inspections of the Andover facility in 2009, 2010 and 2013 revealed QS violations including problems with design controls, process controls, CAPA action and complaint handing.

Shutterstock: oleschwander

FDA staff issued FDA-483s to Philips after each of the eight inspections, the complaint decree states. The agency also sent Philips warning letters linked to the manufacturing plant violations in 2009 and 2011, and met with Philips staff to discuss ongoing corrective actions at both plants on several occasions in 2010, 2011, 2013, 2014 and 2015.

"Although Philips has acknowledged some deficiencies regarding compliance with the QS regulation and promised corrective action, defendants' responses to date do not adequately address the violations observed," the complaint concludes.

Under the terms of the consent decree, Philips must hire a third-party good manufacturing practices expert to inspect the facilities and ensure they meet quality system requirements. After the expert provides their findings to FDA, the agency itself must re-inspect both facilities and provide a written go-ahead before Philips will be allowed to resume production.

The decree further requires Philips to recall AEDs manufactured with the R92 resistor made by Internal Resistive Company, as well as all Q-CPR meters. Philips will provide refurbished exchange units to owners of external defibrillators that are still under warranty, while customers whose devices are no longer under warranty may be eligible for a trade-in rebate.

The company may still distribute AEDs manufactured solely for overseas use or for clinical trials, as long as they are properly marked.

Philips has said it hopes to resume the AED production in 2018, and that the production halt will impact earnings in the fourth quarter of this year and into next year. The combined sales of the external defibrillator product lines affected by the terms of the decree were approximately €35 million per quarter in 2016, according to the firm.

"Let me stress that there is no concern on product quality," Philips' CEO Frans van Houten said during the firm's Oct. 23 third-quarter earnings call. "And over the last years, we've made significant progress in our quality management system regulation compliance."

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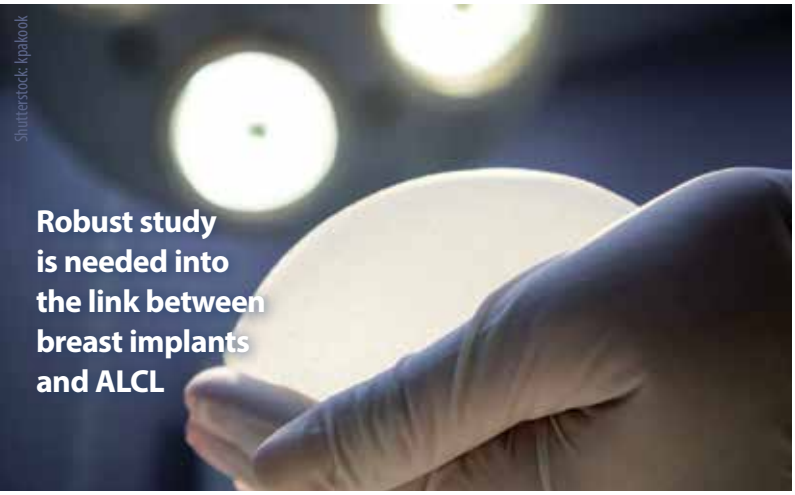
More Study Needed Into Breast Implant Cancer Link, Says EU Safety Committee

NEENA BRIZMOHUN neena.brizmohun@informa.com



The European Commission safety committee SCHEER is calling for a more in-depth evaluation of the possible association between breast implants and anaplastic large cell lymphoma (ALCL), after deciding the latest, albeit limited, evidence on the matter suggests there is a link.

Separately, SCHEER (Scientific Committee on Health, Environmental and Emerging Risks) does not believe there is sufficient evidence to warrant updating its 2014 opinion on the safety of silicone breast implants made by Poly Implant Prothèse (PIP). (The 2014 opinion on the safety of PIP breast implants was published by the European Commission's safety committee SCENIHR. SCENIHR and another of the commission's safety committees, SCHER, merged last year to form SCHEER.)

The SCHEER's advice on both the ALCL link and the 2014 PIP opinion were published late last month. The committee had been asked by the commission to evaluate the latest information available on both topics.

Regarding the possible association between breast implants and ALCL, SCHEER performed a literature search and launched a call for information to determine whether sufficient scientific information was available to conduct a full risk assessment on a possible link.

It found that there had been new documented cases of ALCL in women with breast implants worldwide, suggesting that implants may be associated with an increased risk for ALCL. But it said that the scientific information it retrieved from the literature search and the call for data consisted mainly of case reports, case series and few observational epidemiologic studies. As such, "there is currently insufficient scientific information available to establish a methodologically robust risk assessment to investigate a possible association of breast implants with ALCL development," the committee said.

SCHEER said there was an emerging need for prospective studies to be able to perform a more in-depth evaluation of an association between breast implants and ALCL, and recommended that such an evaluation be carried out.

Moreover, it said that the lack of registries around the world of women with breast implants was a major challenge to providing evidence-based conclusions on the potential association between the implants and ALCL. "Such registers, and their systematic evaluations, are urgently needed."

NO PIP OPINION UPDATE NEEDED

As for PIP breast implants, the committee said that the information it had gathered did not warrant an update of its 2014 opinion on these implants.

SCHEER's literature review showed that new information was available regarding the possible health effects of PIP breast implants, but this information was "rather limited," the committee said. In addition, its public call for information did not result in the submission of scientific papers regarding health effects specific to PIP implants, but rather on breast implants in general.

"New scientific information was found relating to the early and increased PIP implant rupture risk, which suggested that the risk was probably due to the low quality of the implant's shell as already reported in [the] 2014 Opinion," the committee said. "Based on new data, the rupture rate of PIP silicone breast implants was calculated to [be] about 23%, which is similar to the 25%-30% rupture rate indicated in the 2014 Opinion."

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DIGITAL HEALTH IN THE EU:

What Are The New Rules And Reimbursement Challenges?

AMANDA MAXWELL amanda.maxwell@informa.com

EU national authorities are struggling to grasp how to regulate apps and other digital health products. But before they have had the chance to gain full confidence about their responsibilities and how to carry out them out, new requirements are on the way in the form of the EU Medical Devices Regulation.

Added to this is the challenge of the reimbursement systems that exist within the different countries. These systems appear to be at an even more preliminary stage that the regulatory frameworks. *Medtech Insight* spoke with attorney Alexandre Regniault, an associate partner at the law firm Simmons & Simmons in Paris, about some of the details of EU regulatory and reimbursement challenges for digital health.

Medtech Insight: What are the biggest regulatory challenges for apps and other digital health products at present under the EU Medical Devices Directive?

Alexandre Regniault: The main issue today for the sector is to determine whether an app or digital product falls within the scope of the Medical Devices Directive. This generally requires conducting a medical and a technical assessment of the functionalities of the app or digital product. It is also worth noting that in France, the national authorities are not quite ready to allow the reimbursement of mHealth products. Indeed, national authorities are generally not yet convinced of the usefulness of the connected app or mHealth device – and it is up the medical device companies to demonstrate the added value to the patient when applying for reimbursement of their products. Also, the procedures for applying for reimbursement are quite long and could be an obstacle to market access for some products, whose life-time span is shorter than for non-digital medical devices. This is particularly challenging for the many companies in this area that are SMEs: The challenges related to funding and finding the right contact to submit their funding application in the public and the private sector are particularly acute since they do not necessarily have the resources to navigate the system.

> "A reassessment of the digital products will be necessary to determine whether they fall within the scope of the category of medical devices – and, if so, what class they fall into."

How should companies go about managing these challenges?

Regniault: For the moment, companies will need to wait for progress to be made by national authorities and in terms of the implementation of assessment criteria specific for digital products – especially for reimbursement. One step was made last year in France with the first authorization for reimbursement awarded to a digital medical device; this was an app used as part of a telemedicine service for diabetic patients to help them monitor their insulin dosage. However, the French national authority in charge of deciding the reimbursement of medical devices ("CNEDiMTS") limited reimbursement to the use for type 1 diabetic patients – to whom specific training on the use of the medical device should be delivered. For the [more numerous] type 2 diabetic patients, CNEDiMTS considered there was insufficient data available to assess whether the digital product could contribute to the improvement of the patients' medical condition. Some companies believe that existing funding and reimbursement guidelines are not appropriate for the assessment for digital health products and that constitutes an obstacle for their reimbursement via

the social security system But there are developments on the way with CNEDiMTS recently announcing that it will draft dedicated guidelines for the assessment of health connected devices with the view of their reimbursement.

What are likely the biggest regulatory challenges specific to apps and other digital health products under the new Medical Devices Regulation?

Regniault: The MDR will increase the requirements in terms of clinical evaluation. With the entry into application of this text on May 26, 2020, a reassessment of the digital products will be necessary to determine whether they fall within the scope of the category of medical devices – and, if so, what class they fall into. In addition, the MDR will reinforce the obligations of the various operators in the manufacturing and distribution chain. One of the challenges will be to determine who should be considered as the manufacturer and as the distributor of the device. Another challenge will be the post-market monitoring of the medical device, and the requirement to notify any incident regarding its safety. Today, cyberattacks are mainly targeted against IT systems of major companies or administrations. However, the risk of cyberattacks on medical devices is possible, and it is up to medical device companies to implement sufficient safeguards to prevent possible attacks. Many companies will need support to meet the new clinical evaluation requirements and to maximize the use of pre-existing data in this respect.

What proportion of these products needs to be reviewed by a notified body?

Regniault: Before the MDR, companies were able to perform self-certification for class I medical devices – into which many apps, for example, fall – for which a review by a notified body was not required. With the MDR, those class I products will need reassessing to see whether the qualification as a medical device – and the class – is still valid under the new regulation or whether the product should be reviewed by a notified body.

Is there sufficient knowledge and capacity among notified bodies to deal with the demand for reviewing these products?

Regniault: When reviewing digital products or apps, notified bodies have to assess whether the technical specifications of the product are adequate and reliable in terms of security. So, notified bodies will need to cultivate new technical skills and competence to assess the products at a technical level and understand the IT complexity.

Where a notified body is not involved, what are the potential pitfalls for companies?

Regniault: Where a notified body is not involved, companies operating in France are able to refer to the guidelines published by the French National Authority for Health (HAS) on health apps and smart devices (mobile health or mHealth). But manufacturers will have to make their own risk assessment at the technical and medical level, and determine for themselves whether their product should qualify as a medical device. Another aspect to consider would be to determine the respective obligations of the various operators – manufacturer vs. distributor.

How much regulatory work are lawyers having in this field now? Is this likely to grow and, if so, why?

Regniault: As lawyers, we assist our clients during the process of preliminary assessment of the digital product to assess its qualification as a medical device and its risk class. The digital health products sector is a fast-growing sector; companies in the health sector are aware of the necessity to rapidly adapt to the new technologies used by patients in their everyday life. They are also aware that young doctors tend to use new technologies when creating patient-care programs. In addition, more and more studies show the positive effective of digital medical devices in patients' lives, so it is to be expected that an increasing number of new digital products will be designed in the health sector. The question remains, however, whether the social security and national administrations will be also convinced of the usefulness of these products for the national health systems.

What market access challenges are there and in which markets are these the least and the most demanding?

Regniault: Market access challenges that manufacturers might face include showing clinical evidence that the device would improve the patient's life; conducting a medical and clinical analysis to help convince national authorities in charge of reimbursement decisions of the cost-effectiveness of the digital product; determining the requirements under which the digital product/app could be linked to a telemedicine system, for example to allow for videoconferencing; and dealing with national health authorities, such as CNEDiMTS, which are not yet used to performing technical assessments of digital products. Telemedicine has been acknowledged in French law since 2009-2010 but these activities have not quite picked up yet due to difficulties in funding/reimbursement. The current draft social security budget law (PLFSS 2018) is trying to address this.

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US Senators Press Agency Witnesses On Adding UDIs To Claims Forms

SUE DARCEY sue.darcey@informa.com

It's a "no-brainer" that the US Medicare agency should make certain that a line for Unique Device Identifiers (UDIs) is added to Medicare claims forms, Sen. Elizabeth Warren, D-Mass., told the US Center for Medicare and Medicaid Services Chief Medical Officer Kate Goodrich at an Oct. 31 hearing.

The primary thrust of the Senate Health, Education, Labor and Pensions Committee (HELP) hearing was to scrutinize government progress in implementing electronic health record (EHR) reforms required under the 21st Century Cures Act, enacted in December 2016. Both Warren and the committee's Ranking Member Patty Murray, D-Wash., said the transferability of device information through EHRs would be enhanced if information identifying medtech products were required on the claims forms.

"This should be a no-brainer," Warren told Goodrich. "Your own agency's watchdog, the Office of Inspector General, says you should do it, MedPAC [Medicare Payment Advisory Committee] says you should do it, organizations that represent orthopedic surgeons, cardiac surgeons and thoracic surgeons all say you should do it … don't you agree with the Inspector General's recommendation, that adding device identifiers would help reduce Medicare costs and help protect beneficiaries from unnecessary cost and pain?"

Warren was referring to recommendations made by the Department of Health and Human Services' OIG's Oct. 2 report, "Shortcomings of Device Claims Data Complicate and Potentially Increase Medicare Costs." The report found that a lack of specific product model information in 10 years' worth of Medicare claims for fixing or replacing seven faulty cardiac devices cost the agency $1.5bn between 2004-2014, and cost Medicare beneficiaries an additional $140m worth of copayments and deductibles. *(Also see "Lack Of Device Identifiers On Recalled Cardiac Devices Cost Medicare $1.5Bn, OIG Says" - Medtech Insight, 4 Oct, 2017.)*

> The Trump administration is "still reviewing" if UDI information should be added to Medicare claims forms, CMS Chief Medical Office Kate Goodrich says.

The Massachusetts senator also pointed out that other senators, including Charles Grassley, R-Iowa, have been pushing CMS "for several years now" to put UDIs on the claims forms, and that Congress first required that all devices be labeled with device identifiers in 2007.

In the prior, Obama administration, Warren told Goodrich, CMS had "been on board," in agreeing that the UDI data should be on claims. *(Also see "Medicare Agency Comes On Board With Adding UDIs To Claims Forms" - Medtech Insight, 18 Jul, 2016.)*

However, Goodrich replied that "while patient safety as related to devices is obviously very important to CMS … as is customary with a new administration, we are still reviewing this policy," and the Medicare agency no longer was certain that the UDI data should be on claims forms.

MURRAY UNDERSCORED DUODENOSCOPE ORDEAL

Sen. Murray, meanwhile, asked OIG Senior Counselor James Cannatti if the watchdog office "still thinks the right course of action" would be to put UDI information on claims.

She added, "My staff's investigation into outbreaks of superbug infections linked to duodenoscopes recommended that inclusion in the claims form would improve patient safety," referring to her office's January 2016 report on duodenoscope safety issues. *(Also see "Scope Firms, FDA Faulted In 300-Page Senate Report Seeking Device Reforms" - Medtech Insight, 14 Jan, 2016.)*

Murray said that HHS's Office of the National Coordinator (ONC) was also working toward getting electronic health records to always reflect UDI information for individual devices used in patients, and Cannatti acknowledged this would be an important advance, as "you could not rely solely on the claims data."

DEMS PUSH INTEROPERABILITY, BUT GOP CITES BURDENS

The primary thrust of the hearing was to oversee how CMS and the HHS' ONC have carried out provisions of the Cures Act directed at electronic health record interoperability – the kind of streamlined interaction between different EHR systems and between EHRs and devices that will be needed if FDA's device center and medtech manufacturers are to successfully implement the National Evaluation System for health Technologies (NEST) program across all hospitals and clinics and gather patients' real-world data from medical facilities and registries. *(Also see "NEST Executive Director: A One Woman Army" - Medtech Insight, 19 May, 2017.)*

The Cures Act contains provisions that amended the HITECH Act of 2009 in two ways. First, it calls on ONC to set up a framework restricting the number of EHR vendors, and banning them from blocking the flow of information from one health system to another. Second, it provides relief for physicians and other providers from some of the regulatory burdens of the "meaningful use" program, which was designed to incentivize health-care facilities to adopt EHR tools.

Sen. Murray told Jon White, HHS deputy national coordinator for health IT, that she was primarily interested in ONC completing its work to "set up and sup-

port a framework for trusted exchange of electronic health information across networks," or interoperability between different institutions' EHRs, and "developing new conditions for certification of the health information technology," as required by Cures.

White reported that ONC is "committed to getting a draft out by the end of the year," on the trusted exchange networks. However, he added that achieving interoperability between them is a difficult task because "all these folks set up frameworks and agreements in a certain way, but there are often variations between their approaches."

White added that the variations between networks "are often there for good reasons," but that the variations mean many of the frameworks "are not interoperable" with each other.

Meanwhile, HELP Committee Chairman Lamar Alexander, R-Tenn., and other Republicans were more concerned that providers are spending too much time inputting data into electronic health records. Providers, they argue, should be given more time to comply with "meaningful use" requirements under the HITECH Act passed by Congress in 2009.

However, he acknowledged in his opening statement, "as we worked on the Cures bill, we learned that in order for most areas of the bill to succeed, it was essential that electronic health records systems work properly."

Alexander pressed the witnesses to get physicians groups and medical societies to work together "to actually reduce the percentage of time doctors spend on EHRs," and said it is particularly critical that HHS meet a Dec. 13 deadline of setting a goal "for what the correct percentage [of physicians' time in documenting their work in EHRs] should be."

Alexander also promised the HELP Committee "will have additional Cures implementation hearings in December, dealing with the research and development of treatments, cures and medical devices, and on the reforms to mental health programs."

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Ultrasonic Aspirator Guidance Requires Warning On Uterine Use

ELIZABETH ORR elizabeth.orr@informa.com

Labeling for ultrasonic surgical aspirator devices must be edited to include a warning against their use to treat uterine fibroids, FDA said in an Oct. 30 final guidance document.

The aspirators are surgical tools that break tissue into tiny bits for removal, and they're widely used across a range of surgical specialties. However, their design allows tissue fragments to escape and spread throughout the body cavity. Aspirators that use suction to help remove tissue reduce, but do not completely mitigate, the risk, FDA says.

The agency believes the benefits of the aspiration treatment outweigh its risks when it is used to reduce the size of malignant tumors. But that risk-benefit calculation flips when the aspirators are used to remove uterine fibroids, because there's currently no way to test whether fibroids are cancerous before surgery. "This risk of cancer dissemination outweighs any potential benefits in this patient population, particularly since there are alternative treatment options available," FDA wrote.

The guidance document further notes that, although the use to remove fibroids is allowed by some aspirator's labeling, FDA is not aware of it happening.

But given the inherent risk, the agency is calling for aspirator device labeling to include a contraindication against their use to treat uterine fibroids. The recommended labeling statement reads: "CONTRAINDICATION: This ultrasonic surgical aspirator device is not indicated for and should not be used for the fragmentation, emulsification, and aspiration of uterine fibroids." Manufacturers should also review labeling to ensure it is consistent with the contraindication; for example, lists of surgeries that may be performed with the use of the aspirator should not include uterine fibroidectomy.

New Labeling Statement

"CONTRAINDICATION: This ultrasonic surgical aspirator device is not indicated for and should not be used for the fragmentation, emulsification, and aspiration of uterine fibroids."

Manufacturers of aspirators cleared with 510(k)s have 120 days to add the contraindication to labeling; submit the current and revised labeling to FDA's device center; and send the updated labeling to existing customers. The change can be made as a 510(k) amendment rather than a new 510(k), the guidance states. Manufacturers submitting new products will also be expected to include the contraindication.

FDA first issued the guidance in draft form in November 2016. *(Also see "US FDA: Ultrasonic Tools Shouldn't Be Used For Uterine Surgery" - Medtech Insight, 14 Nov, 2016.)* It echoes similar concerns about power morcellation devices, which gained a black box warning saying they shouldn't be used to treat most cases of uterine fibroids in 2014. *(Also see "FDA Puts Black Box Warning On Power Morcellators With Immediately-In-Effect Guidance" - Medtech Insight, 24 Nov, 2014.)*

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TCT 2017: New Analysis Finds Edwards' Sapien TAVR Saves $1,000s Per Patient

REED MILLER reed.miller@informa.com

As a further boost to the existing body of data backing **Edwards Lifesciences**'s market-leading Sapien line of transcatheter aortic valve replacement systems, its leading cardiology product, a new cost-effectiveness analysis of Edwards-sponsored randomized trials has shown that TAVR is a highly cost-effective alternative to surgical valve replacement in patients at intermediate surgical risk and can save thousands of dollars over the total course of patient care.

David Cohen from Saint Luke's Mid America Heart Institute in Kansas City and colleagues analyzed the results of the PARTNER 2A randomized trial and the SAPIEN 3 Intermediate Risk registry to develop a patient-level economic analysis of TAVR – with either Edwards' *Sapien XT* or third-generation *Sapien 3* systems – and surgical valve replacement.

Cohen presented the results of the analysis, which was also sponsored by Edwards, at the Transcatheter Cardiovascular Therapeutics scientific symposium in Denver on Oct. 31.

The US FDA approved Edwards' Sapien XT and Sapien 3 TAVR systems for intermediate-risk patients in 2016 and approved rival **Medtronic PLC**'s*CoreValve Evolut* TAVR platform for the same indication earlier this year. *(Also see "US FDA Green-Lights Medtronic's CoreValve Evolut For Intermediate Risk" - Medtech Insight, 11 Jul, 2017.*

Previous analyses of TAVR trials showed the technology is cost-effective, but not cost-saving, compared to medical therapy in in-operable patients and cost-effective compared to surgery in patients with high surgical risk. But this new analysis focused on intermediate risk patients shows TAVR – at least with Sapien valves – is an "economically dominant strategy" compared to surgery, according to Cohen.

"Taken together with the clinical data that we know, these findings suggest that TAVR should be the preferred strategy for these patients, based on both clinical and economic considerations," Cohen concluded.

"The market is already moving this way, so I don't know if this is going to dramatically change the way people are practicing, because the practice is driven right-now by the clinical data, which are already good and by patient-demand, which is high," Cohen said. "Fortunately for surgeons, at least at this point, is that they are involved in all of these procedures because of the way – at least in the US – Medicare has a mandate that all of these procedures be done by a heart team, and so surgeons are very involved…That's been a very good thing for our patients and our practices."

The comparison of TAVR with Sapien XT to surgery was based upon the randomized assignment within PARTNER 2A, but the comparison between TAVR with Sapien 3 and surgery was not randomized. The cost data was compiled from measured resource utilization, Medicare claims for the index hospitalization and follow-up period, or by piecewise regression models.

In PARTNER 2A TAVR procedures with Sapien XT were about two hours shorter, on average, than the surgical procedures (102 minutes vs 236 minutes, p<0.001) and the average hospital length of stay was about four and a half days shorter (6.4 vs 10.9, p<0.001).

Cohen et al. found the direct procedural costs were $22,083 higher with TAVR than surgery in the PARTNER2A intermediate risk patients because of cost the Sapien XT valve costs so much more than any surgical valve, but most of this higher cost was offset by cost-savings created by shorter hospital-stays and the reduction in-hospital complications. The total costs for the index hospitalization were about $2,900 higher with TAVR than surgery ($61,433 vs. $58,545; p=0.014) and, over the following two years, the costs were $9,303 lower with TAVR than surgery.

The total medical care costs were about $6,500 lower with TAVR than surgery over the two-year follow-up period ($107,716 vs. $114,132; p=0.014). Projected over the patients' lifetime, TAVR with Sapien XT in intermediate-risk patients will cost $7,949 less than surgical valve replacement and improve quality-adjusted life expectancy by 0.15 years, Cohen et al. conclude.

The comparison of TAVR with Sapien 3 in the intermediate risk patients in Sapien 3 registry compared to the intermediate-risk surgery patients in PARTNER 2A showed TAVR procedures were about two-and-a-half hours shorter (84 minutes vs. 236 minutes; p<0.001) and the TAVR patients stayed about six fewer days in the hospital than the surgery patients (4.6 days vs. 10.9 days; p<0.001).

The total costs for the index hospitalization with Sapien 3-TAVR were about $4,000 lower than with surgery ($54,256 vs. $58,410; p=0.014) and over the first year of follow-up, the total costs of TAVR with Sapien 3 were about $11,000 less per patient than surgical valve replacement in the intermediate risk patients, according to this analysis.

Over a lifetime horizon, TAVR with Sapien 3 could yield lifetime cost savings of $9,692 per patient and a 0.27 more quality adjusted life-years than surgery in intermediate risk patients.

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TCT 2017: PCI And CABG Yield Similar QOL Outcomes For Left-Main Disease

REED MILLER reed.miller@informa.com

Patients with left-main coronary artery disease (LMCAD) have a better quality of life in the first month after stenting than similar patients treated with coronary artery bypass graft (CABG) surgery, but this difference disappears three years after the procedure, new data from the EXCEL trial show.

Three-year quality-of-life data from EXCEL were reported by Suzanne Baron from St. Luke's Mid America Heart Institute in Kansas City on Oct. 30 at the Transcatheter Cardiovascular Therapeutics (TCT) scientific symposium and published simultaneously in the *Journal of the American College of Cardiology.*

EXCEL randomized patients with LMCAD of low-to-intermediate complexity to PCI with **Abbott Laboratories Inc.**'s *Xience* everolimus-eluting stent or CABG. The primary results from EXCEL, presented at TCT 2016 and published in the *New England Journal of Medicine*, found that rates of death, stroke, and myocardial infarction were similar with both PCI and CABG at a median of three years. *(Also see "TCT 2016: EXCEL And NOBLE Give Different Answers On Stenting Vs. Surgery For Left-Main Disease" - Medtech Insight, 1 Nov, 2016.)*

Of the 1,905 patients with LMCAD in EXCEL, 1,788 participated in the quality-of-life sub-study. Baron and colleagues assessed the patients' quality of life at baseline and at one month, one year, and three years using the Seattle Angina Questionnaire, the SF-12 health survey, the Rose Dyspnea Scale, the Patient Health Questionnaire-8, and the EQ-5D health-related quality-of-life questionnaire.

The PCI patients showed both disease-specific and overall health improvements within a month after their procedure and sustained these improvements out to three years. The CABG patients showed only small improvements 30 days after their surgery, largely due to the physical limitations caused by the sternotomy necessary for CABG. But their quality of life and health scores caught up with the PCI group's over the three years and improved significantly across all scales to the same levels as the PCI group's scores.

"In contrast to previous trials that compared quality of life after CABG vs PCI, we observed no significant differences in long-term health status outcomes between PCI and CABG," Baron said at the conference. " Taken together with the [the previous] three-year clinical data from the EXCEL trial, these results suggest that PCI and CABG provide comparable intermediate term outcomes for appropriately selected patients with left main coronary disease."

Currently, European and US professional guidelines currently provide Class IIa recommendations (indicating the procedure is "reasonable") for PCI to treat LMCAD with low anatomical complexity. In 2012, results of the NIH-sponsored FREEDOM trial showed patients with diabetes and advanced coronary artery disease had better overall outcomes with CABG than PCI, with significantly reduced rates of death and myocardial infarction, but a higher rate of stroke. Results of the SYNTAX trial published in 2013 suggested that CABG should remain the standard of care for patients with complex lesions because it yielded lower rates of myocardial infarction and repeat revascularization than PCI, while PCI would be an acceptable alternative for patients with less complex disease or left main coronary disease.

But these trials were performed with older drug-eluting stent technologies. EXCEL senior investigator David Cohen from St. Luke's Mid America Heart Institute in Kansas City said. "We have done a lot of these analyses and this is the first time we've seen one like this. That's remarkable and a testimony to how far PCI has come that it can now stand toe-to-toe with bypass surgery but also give patients a much more rapid recovery."

Cohen pointed out that the EXCEL quality-of-life sub-study was the first CABG-vs-PCI comparison trial to evaluate patients' self-reported depression scores and that the PCI patients reported lower rates of depression than the CABG patients in the first-year post-procedure. "Depression is a pretty serious thing in these patients. So that's an additional benefit," Cohen said.

Baron explained that the trial results will help patients decide on whether to opt for surgery or PCI. "Patients want to know, 'Am I going to feel better and if I feel better faster, will I pay a price down the road for that?' We do know there's an increase in repeat revascularization [with PCI], but we can now tell them that it won't necessarily – at least for the three years of quality of life data that we have - doesn't affect quality of life."

Roxana Mehran of Mount Sinai School of Medicine in New York suggested that the professional guidelines need to be updated to reflect these quality-of-life data. "Guidelines are usually driven by clinical endpoints, not quality of life, but hopefully we can change that because I do think this is an incredibly important area for our patients to be in shared decision-making."

These data "vindicate the decision-making of patients [who chose PCI]," said Jonathan Hill of Kings College Hospital in London. "This is a very important study," he said. "Because it legitimizes us asking the question about behavior that is avoiding the sternotomy. We must not underplay it. We're comparing days of recovery time [with PCI] to months or up to a year of recovery time [with CABG]."

He suggested that quality-of-life measures like the ones used in this EXCEL sub-study be applied to all multivessel coronary revascularization trials.

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CONTINUED FROM PAGE 5

TABLE 1

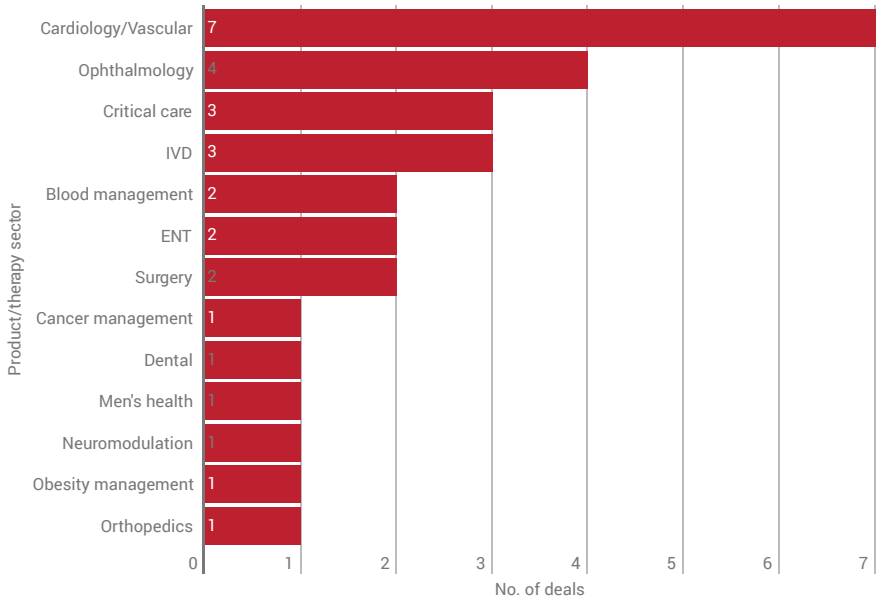
Top 5 VC Fundraisings, October 2017

RANKING	COMPANY	BASED IN	PRODUCT/ THERAPY SECTOR	AMOUNT RAISED	FINANCING ROUND	TOTAL INVESTMENT
1	NeuroPace	CA, US	Neuromodulation	$74m	Series F	$294m
2	Shockwave Medical	CA, US	Vascular	$35m	Part of a larger Series C	$136.5m
3	Azura Ophthalmics	Tel Aviv, Israel	Ophthalmology	$16m	Series B	Undisclosed
4	CathWorks	Kfar Saba, Israel	Cardiology/Imaging	$15.8m	Series B	Undisclosed
5	TELA Bio	PA, US	Surgery	$15m	Undisclosed	Undisclosed

Source: Medtech Insight VC deal tracker

FIGURE 3

No. Of Deals By Product/Therapy Sector, October 2017



Source: Medtech Insight VC deal tracker

ings. (See Table 1.) While there was one deal in October that raised over $50m, NeuroPace's $74m Series F, the second largest fundraising was only half that amount, $35m from Shockwave Medical. Thereafter, the top fundraisings were just in the mid-teens range.

NeuroPace Inc. 's $74m round brought in new investors KCK Group, a family investment fund, and Orbimed, a well-known name in the health care investment community. The Silicon Valley company said it will use the funds to accelerate commercialization of its *RNS system*, a closed loop, cortical stimulation system approved by the US FDA to treat patients with refractory epilepsy. Unlike **LivaNova PLC** 's VNS system, another established neuromodulation product in the epilepsy market, NeuroPace's RNS system senses abnormal brain activity and then delivers electric shocks to a target point in the brain cortex before the epileptic seizure occurs. The VNS system, on the other hand, stimulates the vagus nerve system and is programmed to deliver neurostimulation at regular intervals.

CLICK

For more details about VC deals go to *Medtech Insight*'s VC Deal Tracker: http://bit.ly/2ztwiLc

NeuroPace got the FDA premarket approval in November 2013 and has been building a body of evidence to back the technology before ramping up commercialization. To date, around 1,300 patients in the US has received the system and results from multiple controlled, prospective studies have shown that 72% median seizure reduction patients experienced seven years after initiating the therapy, including 30% of patients who experienced seizure reductions of 90% or greater.

HEART AND EYES

In terms of product/therapy sectors that grabbed investors' attention in October, IVD again fell from its usual top position, giving way to cardiology/vascular, which took seven deals, and ophthalmology, with four deals. (See Figure 3.)

Indeed, looking at across the different product sectors that have successfully completed financing rounds this year so far, cardiology/vascular has just pipped IVD to the post with 45 deals (versus 44 for IVD). Ophthalmology, a market with a significant growth opportunity primarily driven by the ageing population, will likely be in the top five. But, as with the total deal value, there are still two more months to go before the end of the year and whether IVD keeps its long-held leading position as most popular investment space or whether there might be new sectors in the top spots remain to be seen.

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CONTINUED FROM PAGE 1

While intragastric balloons accounted for the second-largest segment with a 46% global market share, this segment is expected to see the biggest growth over the forecast period at a CAGR of 32.9%, from $63.6m in 2016 sales to $263.9m by 2021.

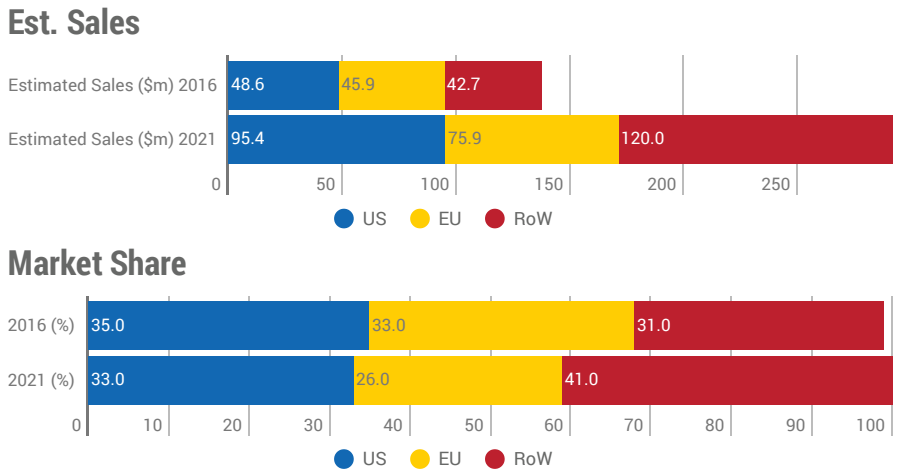
The smallest segment, implantable neuroregulators and gastric stimulators, made up only slightly more than 1% of the overall market in 2016. However, *Meddevicetracker* expects that these innovative technologies will see significant growth, nearly doubling revenues at a CAGR of 15.7% from $1.3m in 2016 global sales to $2.7m by 2021.

On a regional basis, the US dominated the weight-loss devices market in 2016 with a 35% market share and $48.6m in global sales, which is expected to reach $95.4m in sales by 2021. The five major European countries (France, Germany, Italy, Spain and the UK) accounted for 33% of the global market in 2016 with $45.9m in sales, which is expected to climb to $75.9m by 2021. The emerging countries, which accounted for a 31% market share in 2016, are expected to see the highest growth from $42.7m in 2016 sales to $120m by 2021, which is due to the rising obesity rates countries such as Brazil and Mexico. (See Figure 2).

FIGURE 2

Minimally Invasive Weight-Loss Devices Market, Estimated Share By Region, 2016-2021

Market share may not equal 100% due to rounding. EU are five major EU markets (France, Germany, Italy, Spain, UK); RoW=rest of world



Source: "Minimally Invasive Weight Loss Devices Market," Meddevicetracker

INTRAGASTRIC BALLOONS: OVERVIEW

The dramatic decline in LAGB procedures has benefitted the intragastric balloon market along with patients' demand for and greater access to minimally invasive procedures.

For years, moderately obese patients with a body mass index of 27-35kg/m2 really had nowhere to go, said Julie Ellner, a bariatric surgeon in solo practice in San Diego. Not being eligible for sleeve gastrectomy, LAGB or gastric bypass surgery, it wasn't until the arrival of intragastric balloons that surgeons like Ellner were able to offer these patients an alternative.

"I thought the balloons would be great for patients with a lower BMI who don't qualify for surgery, who needed help, because these patients have been coming to me for years, asking 'what can I do?' and every year, I had to look at them and say there's really nothing," Ellner told *Medtech Insight*. As a long-time bariatric surgeon, Ellner said she was initially skeptical, but after implanting some 50 balloons, she's become a believer.

"I am shocked at how well these patients are doing," she said. "Patients report

"I thought the balloons would be great for patients with a lower BMI who don't qualify for surgery, who needed help, because these patients have been coming to me for years, asking 'what can I do?' and every year, I had to look at them and say there's really nothing," Ellner says. "I am shocked at how well these patients are doing. Patients report appetite suppression as soon as they get that balloon at the same level as patients who get gastric bypass surgery."

Julie Ellner, San Diego bariatric surgeon

Photo credit: Julie Ellner

appetite suppression as soon as they get that balloon at the same level as patients who get gastric-bypass surgery." She said she expected the balloon to help with portion control, but didn't expect it to be so profound for appetite suppression.

Intragastric balloons fill a niche for a moderately obese population with a body mass index of 27-40kg/m2 not eligible for gastric bypass, sleeve gastrectomy and LAGB. Intragastric balloons are designed to fill up space in the stomach to induce a feeling of fullness or satiety to help patients eat less and lose weight.

Similar to restrictive gastric procedures such as LAGB, these devices have been designed to reduce the stomach's capacity, but use an inflatable space-occupying balloon filled with saline or air that is inserted "non-surgically" or endoscopically via the esophagus to the stomach.

These devices typically remain in the stomach for up to six months, upon which they are removed, which requires a second procedure. While most patients return to normal activities the same day after an intragastric balloon implantation, the procedure is only a short-term solution and results in less dramatic weight reduction compared to LAGB or gastric bypass.

COMPETITIVE LANDSCAPE

In the US, intragastric balloons have seen rising adoption since 2015 with the FDA approval of two products – **Apollo Endosurgery Inc.**'s *Orbera* and **ReShape Medical Inc.'s***Integrated Dual Balloon System*, the latter of which was acquired by **EnteroMedics Inc.** for $61.1m in cash and stock *(Also see "EnteroMedics Inflates Neuromod-Obesity Offering With ReShape Balloon" - Medtech Insight, 4 Oct, 2017.)*.

EnteroMedics announced on Oct. 3 it bought ReShape to extend its obesity product line by adding another minimally-invasive FDA-approved product for treating obesity. Following this acquisition, on Oct. 23, EnteroMedics said it was rebranding itself as **ReShape Lifesciences**.

Today, there are six balloon systems on the market. (See Figure 3, Table 1.)

Apollo's Orbera was the first system to win the CE mark in 1997. It was sold outside of the US in 2004 before winning US FDA approval in 2015. On Aug. 30, Apollo announced it gained approval to CE mark its newest balloon, the *Orbera365 Managed Weight Loss System*, which doubles the in-dwell period from six months to 12 months. The Orbera365 is expected to hit the market during the fourth quarter of 2017. Obera is inserted endoscopically in a 20-minute procedure and remains in the stomach for up to six months, upon which it requires a second procedure to deflate and remove it.

With more than 277,000 systems implanted, the Obera system remains the world's best-selling system. In 2016, Apollo led the global intragastric balloon market with a 42.6% global share and estimated sales of $27.1m.

Orbera's biggest rival in the US is ReShape Medical's Integrated Dual Balloon System, the first and only temporary dual balloon system that comprises two connected saline-filled balloons that are attached to each other via a flexible tube.

In recent clinical trials, the ReShape system has shown an average weight loss of 25%, or one-quarter of excess weight over six months. The company claims that it is the only balloon system designed to prevent intestinal obstruction, or migration of a deflated balloon from the stomach into the intestines.

The ReShape system has been available in Europe since 2011 before it was approved in the US in 2015 and has made inroads in other parts of the world including Mexico, which has one of the highest obesity rates worldwide. Globally, ReShape was the third-leading supplier in this market segment with an 18.1% market share and about $11.5m in sales in 2016, behind **Spatz FGIA.**

In 2016, Apollo and Reshape were the only players in the US market. Apollo led the US market with a 70.7% market share and $13.3m in sales with Reshape accounting for a 29.3% market share and $5.5m in sales.

Recent FDA approvals and growing competition from balloon systems made by four other companies – **Hélioscopie**, **Allurion Technologies Inc.**, Spatz FGIA and **Obalon Therapeutics Inc.** – are expected to cause a shift in the competitive landscape in the US in coming years.

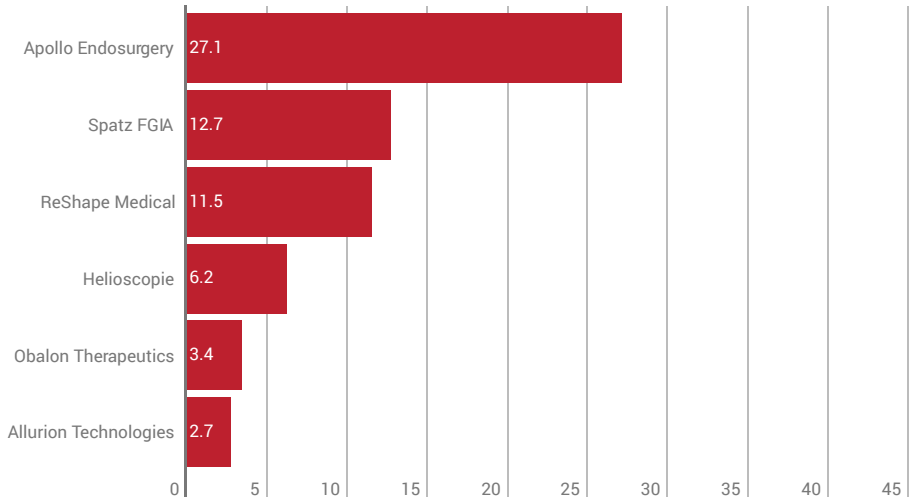
And recently issued safety reports by the FDA regarding balloon systems, in particular, referring to those made by ReShape and Apollo, could also have a significant impact on future intragastric balloon sales in the US.

FDA Safety Concerns

The FDA issued a warning letter in February stating it received two different types of adverse events, over-inflation (with fluid/saline) and acute pancreatitis, which required immediate device removal *(Also see*

FIGURE 3

Balloon Systems Global Market, Share By Supplier, 2016



Source: "Minimally Invasive Weight-Loss Devices Market," Meddevicetracker

"US FDA Warns Docs On Gastric Balloon Adverse Events" - Medtech Insight, 9 Feb, 2017.).

In August, the agency then issued another safety alert saying it received "five reports of unanticipated deaths that occurred in 2016,"; one report involved ReShape's Integrated Dual Balloon System and four reports involved Apollo's Orbera system.

The FDA stressed that it didn't know what caused the deaths, stating: "At this time, we do not know the root cause or incidence rate of patient death, nor have we been able to definitely attribute the deaths to the devices or the insertion procedures for these devices." The agency noted that there were two additional reports of death between 2016 related to potential complications associated with balloon treatment: One involved gastric perforation with Orbera and the other involved esophageal perforation using the Integrated Dual Balloon System.

Apollo on Aug. 10 issued a statement stating that it self-reported all five cases to the FDA as part of its Global Product Surveillance program and stated that since it gained FDA approval in 2015, it had an incident rate of less than 0.01%. Since the balloon system was introduced worldwide in 2016, the company recorded 21 deaths out of 277,000 balloons distributed *(Also see "Gastric Balloon-Makers Respond To US FDA Warning" - Medtech Insight, 14 Aug, 2017.)*.

Ellner said she called Apollo after receiving the FDA safety alert and was told by company officials that there is no indication that the balloon was the cause of death and applauded the company for self-reporting incidences and doing worldwide surveillance.

"One of the problems I've always faced is patients asking what's going on in other countries and why can't we go to Mexico, Canada or South America to get something done," Ellner said. "One of the problems we face internationally, is that things aren't tracked that well, so kudos to Apollo for really tracking all of their balloons worldwide."

ReShape told CNN it is "committed to supporting the continued safe and effective use of the dual balloon and is proactively communicating with physicians about this FDA update. Patients with questions about this FDA update should contact their physicians directly." EnteroMedics Inc. didn't comment on the safety issue in its October announcement of the ReShape acquisition.

"One of the problems I've always faced is patients asking what's going on in other countries and why can't we go to Mexico, Canada or South America to get something done," Ellner says. "One of the problems we face internationally, is that things aren't tracked that well, so kudos to Apollo for really tracking all of their balloons worldwide."

Ladenburg Thalmann & Co. Inc.'s analyst Jeffrey Cohen, who wrote a recent analysis on EnteroMedics, also declined to comment on the FDA safety alert, but he remains bullish on the future of balloon sales.

In his research note on EnteroMedics from Oct. 4, Cohen wrote that ReShape's revenue was about $4m for 2017 with the fourth quarter being integrated into EnteroMedics' revenue. He also wrote that EnteroMedics "anticipates a growth rate of 40% as gastric balloons in general have only been approved for about two years (in the US) and is in the early phase of market awareness (only accounting for approximately 10% of procedures annually)." This is a more optimistic growth rate than the 32.9% CAGR forecasted by *Meddevicetracker*.

NEWEST GENERATION BALLOONS

Apollo Endosurgery is not sitting on the sidelines. The company recently announced it will introduce a longer-duration Orbera that essentially doubles the implantation period from six months to one year *(Also see "OUS Approvals Analysis: Medtronic, MicroPort Lead August's Line-Up Of International Approvals" - Medtech Insight, 14 Sep, 2017.)*. The new Orbera365 balloon system is expected to increase average weight loss due to the extended therapy period. *Meddevicetracker* expects the new system will bolster sales following its expected launch in the last quarter of this year.

Meanwhile, a number of smaller companies, including Obalon Therapeutics' *Obalon*, which was introduced in the US this January, and Allurion Technologies' CE-marked *Elipse*, are hoping to make inroads with their innovative technologies.

Carlsbad, California-based Obalon Therapeutics' Obalon system won the CE mark in Europe in 2012 and gained FDA approval in September 2016. It made its debut in the US this January based on the success of the randomized, sham-controlled pivotal SMART study of 387 adults with a BMI range of 30-40. In the study findings, the Obalon group had nearly double the weight loss vs. the sham-controlled group as well as statistically significant improvements in metabolic profiles.

The Obalon system was also the first FDA-approved three-balloon, air-filled system for weight loss that is swallowed in a capsule. What makes this balloon unique is that it is attached to a thin 1mm detachable inflation microcatheter that remotely inflates the balloon in a 10-minute procedure requiring no sedation. Patients can swallow up to three balloons during a three-months treatment period to stimulate additional weight loss, but all balloons must be removed six months after the first balloon is implanted in a 15-minute endoscopic procedure.

Ellner said while the technology sounds intriguing, she has reservations about a balloon that comes in a capsule form.

"When I put the Orbera balloon in, I've done an endoscopy and am in the patient's stomach with the camera and I can see if there are any abnormalities in the stomach lining that would indicate I shouldn't put this balloon in," she noted. "If you're swallowing a capsule, you may have pre-ulcer, gastritis or something genetically abnormal where you shouldn't have a balloon in place." She said she has seen cases where

patients had abnormally shaped long and skinny stomachs where she had to customize the balloon size to ensure the balloon doesn't rub on the sidewalls of the stomach.

"The Orbera can be customized based on what you see in the endoscopy, which allows physicians to do the best evaluation possible before putting the balloon in a patient," she said.

She also had concerns about an air-filled system, which she said, may float on top of the stomach fluid and cause gas pain.

"It could also intermittently block the entrance of the esophagus into the stomach vs. the saline-filled balloon, which moves with the fluid in the stomach the way the stomach naturally moves fluid back and forth," she said.

One of the perceived benefits of Allurion's Elipse system over others is that it naturally deflates at the end of the four-months treatment period and is then excreted, which according to the company, lowers potentially dangerous complications and costs. The fluid-filled balloon gained the CE mark in December 2015 and is not yet FDA approved.

Ellner, however, feels that complications could potentially be possible, if the balloon gets caught up in the intestines.

"I would worry about what kind of material that balloon is made out of and if it is really going to pass all the way through the rest of the intestinal tract," she said. "There are a lot of different places in your intestines where a deflated balloon could get potentially hung up and cause bowel obstruction."

She said those are the things that doctors and the FDA are likely to look at when evaluating this balloon system.

Provided Elipse wins FDA approval and hits the US market soon as expected, it would compete directly against Obalon.

While both Obalon and Allurion contributed only about 5.3% and 4.2% of the global market share in 2016 based on initial sales outside of the US of nearly $3.4m and $2.7m respectively, they are expected to have growth potential thanks to their innovative, proprietary technologies

The second-leading global supplier in 2016 with a 20% market share and about $12.7m in sales, Great Neck, New York-based Spatz FGIA, also stands out with its

TABLE 1

Intragastric Balloon Systems, 2017

COMPANY	PRODUCT	DESCRIPTION
FDA-APPROVED AND CE-MARKED SYSTEMS		
Apollo Endosurgery	Orbera	Leading intragastric balloon system. Saline-filled, inserted endoscopically in a 20-min. procedure and may remain in the stomach for up to six months. Requires second procedure to remove. Has been used in more than 220,000 patients.
Obalon Therapeutics	Obalon	First FDA-approved three-balloon, air-filled system for weight loss that is swallowed in a capsule. Up to three balloons can be swallowed and inflated during a three-months treatment period to stimulate additional weight loss. All balloons must be removed six months after the first balloon is implanted.
ReShape Medical	ReShape Integrated Dual Balloon System	First and only temporary "dual-balloon" device. Unique design comprising two connected saline-filled balloons. Design is claimed to prevent intestinal obstruction.
Available outside the US		
Allurion Technologies	Elipse	First intragastric balloon that is swallowed and naturally excreted without anesthesia, endoscopy or surgery (the balloon naturally deflates at the end of the four-month treatment period and leaves the stomach, where it transits the GI tract and is excreted). Filled with fluid vs. air.
Helioscopie	Heliosphere BAG and Helisphere BAG Pre OP	Designed to be lighter and more comfortable than competitive systems; balloon is filled with air instead of saline and as a result claimed to be better tolerated and reduce side-effects (limiting post-implantation nausea and vomiting) by about 80%
Spatz FGIA	Spatz3 Adjustable Balloon System	First and only adjustable intragastric balloon that is CE approved for implantation for up to one year; adjustability allows physicians to add volume to the balloon and facilitate additional weight loss; saline-filled

Siource: "Minimally Invasive Weight Loss Devices Market," Meddevicetracker

TABLE 2

Implantable Electrical Stimulators/Neroregulators For The Treatment Of Obesity, 2017

COMPANY	PRODUCT	DESCRIPTION
EnteroMedics	Maestro Rechargeable System	Uses proprietary vBloc therapy to transmit high-frequency, low-energy electrical impulses that block messages conveyed by the vagus nerve, which aid in the contraction of stomach muscles and intestines to help process food and are believed to be involved in feelings of satiety and hunger.
MetaCure	DIAMOND (formerly the TANTALUS)	Rechargeable implantable gastric stimulator that uses electrodes to automatically sense and monitor the natural activity of the stomach in real time and apply gentle electrical stimulation (gastric contractility modulation (GCM) to the stomach during mealtime to induce satiety.

Source: "Minimally Invasive Weight Loss Devices Market," Meddevicetracker

one-year, saline-based *Spatz3 Adjustable Balloon System*.

The balloon system is the only CE-marked system that can be implemented for one year, twice as long as competitive systems, and has seen good growth internationally. Another benefit is its adjustability, which allows doctors to add volume to the balloon to facilitate additional weight loss. The company announced last February it has been steadily expanding market share in Mexico (since its approval in 2015), a country with one of the highest obesity rates worldwide that is also a growing market for "medical tourism."

Hélioscopie was the fourth-leading global supplier of intragastric balloons in 2016 with a 9.7% market share and $6.2m in sales. The French company claims its *Heliosphere* balloon is more comfortable and lighter than competitive systems because it is filled with air instead of saline. This makes the device easier to tolerate and reduces post-implantation nausea and vomiting by about 80%, according to the company.

Hélioscopie makes two intragastric balloons: the *Heliosphere BAG* and *Heliosphere BAG Pre OP*, which serves as a temporary system for pre-operative treatment of morbid obesity. The company said in five clinical trials of more than 670 patients, measured weight loss was between 9kg and 24kg (19.8-52.9 lbs) with 12-16% of patients experiencing vomiting for more than eight days, with a mean duration of vomiting at less than three days.

Similar to the LAGB segment, the intragastric balloon segment certainly has its challenges. For one, although severe complications are rare, they can include potentially dangerous bowel obstruction, gastric perforations and in very rare cases, death.

Challenges

According to the American Society for Metabolic and Bariatric Surgery, a review of the original *BioEnterics Intragastric Balloon (BIB)* system (which is now Orbera) reported a very low treatment-related mortality rate of 0.07% as a result of post-insertion bronchoaspiration and gastric perforation in patients with previous fundoplication, which highlights the importance of careful patient selection.

In a review entitled "Evidence-based review of the Bioenterics intragastric balloon for weight loss" that appeared in the Obesity Surgery medical journal, Jean-Marc Dumonceau wrote that although post-insertion mortality rate was extremely low, severe complications were exceptional (gastric perforation and intestinal obstruction were observed at rates of 0.2% each) and digestive intolerance led to early BIB removal in 2.5% of patients. Apollo Endosurgery acquired BIB in its December 2013 acquisition of Allergan's obesity intervention line.

To date, safety and efficacy data of intragastric balloons are limited and the most relevant current data stems from two pivotal US trials that led to the FDA approval of the Orbera and ReShape systems.

Data for the Orbera trial showed a mean 38.4% excess weight loss at six months, and results of the REDUCE pivotal trial for the ReShape balloon revealed a mean 28% excess weight loss. Both gastric balloon systems showed statistically significant and greater weight loss compared to the control group.

That said, the lack of insurance reimbursement makes both procedures costly. Procedure cost with the Obalon three-balloon system, including balloon removal, runs $6,000-$9,000; estimates for Orbera or ReShape, including the device cost and cost of the second removal procedure, range from $8,000-$13,000. This is also the reason why "medical tourism" to lower-cost markets such as Mexico is growing.

There is also an increased risk of adverse events that occurs when patients are being "lost to follow-up," which increases the risk of leakage and passage of the balloon into the intestine, or intestinal obstruction.

Advantages

One of the biggest advantages of intragastric balloons is that they fill a need of a currently underserved population of obese people with a BMI between 30 and 40 who fail conservative diet, lifestyle changes and prescription weight loss drugs and are not eligible, or do not want to endure, highly invasive and permanent anatomy-altering bariatric surgery. The procedure is minimally invasive and leaves the stomach anatomy intake and is also reversible while improving co-morbidities such as Type 2 diabetes and hypertension.

IMPLANTABLE NEUROREGULATORS AND GASTRIC STIMULATION SYSTEMS

In the emerging minimally invasive implantable neuroregulatory segment, there were only two competitors in the global market in 2016: EnteroMedics, which pioneered the implantable *vBloc therapy* (vagal blocking for obesity control therapy) and monopolizes the US market with its *Maestro Rechargeable System* and Israel-based **MetaCure Inc.**'s *DIAMOND gastric stimulation therapy, currently* sold only outside of the US. (See Table 2.)

EnteroMedics is the global leader with estimated Maestro vBloc system sales approaching $800,000 in 2016, accounting for a 61.5% global market share. The company gained FDA approval in 2015 and has been selling its device to selected approved Bariatric Centers of Excellence in the US, though this process has been slow. The conservative growth strategy calls for expanding its direct sales force, surgeon training and obtaining payer support.

MetaCure's DIAMOND system achieved sales of about $500,000 in 2016 with a market share of 38%. The system has shown success in improving glycemic control and achieving sustainable weight loss, and is capitalizing on treating both conditions.

However, EnteroMedics is now also targeting "diabesity", or patients with both Type 2 diabetes and obesity, and may soon compete with MetaCure internationally.

EMERGING TECHNOLOGIES

When it comes to emerging technologies that will compete with minimally invasive bariatric therapies, such as intragastric balloons, there are several smaller players with devices in clinical trials. Some have obtained regulatory approval and are already on the market. Others are expected to hit the market over the next three to five years. The following six technologies rank among them and are on *Meddevicetracker's* watch list.

Aspire Bariatrics

Aspire Bariatrics Inc.'s *AspireAssist* is considered unappealing by many as it reduces calorie intake by aspiration *(Also*

see " Stomach-Draining Device Taps Into Minimally Invasive Bariatric Surgery Space " - Medtech Insight, 15 Jun, 2016.).

During a 15-minute procedure, a thin tube is placed in the stomach that connects the inside of the stomach to a "button valve" on the outside, which allows the patient to literally empty up to 30% of a meal into a toilet. The procedure is indicated for adults with a BMI of 35-55 who have failed conservative therapies. AspireAssist gained the CE mark in 2011 and FDA premarket approval last June and is currently marketed in the US, Europe, Australia and New Zealand. The company hopes to obtain insurance coverage in the US based on trial results.

According to the company, the AspireAssist can result in 37% excess weight loss at one year based on US PATHWAY trial results, which is comparable to gastric banding (also 37% EWL), but less than gastric bypass (64%) and sleeve gastrectomy (55%).

But Ellner said that she wouldn't recommend this device to any of her patients for multiple reasons.

"It's basically surgically induced bulimia," she said. "What we're trying to do with surgery and with the balloons is to teach people how to make healthy decisions and how to have a healthy relationship with food and the AspireAssist doesn't do that." Her other concern is that the device suctions out electrolytes and nutrients that our body makes to help normal digestion.

The company, however, claims that since only one-third of consumed food is being aspirated, the body still gets adequate nutrients and said that patients receive counseling to learn how to eat more healthfully.

BarioSurg/EnteroMedics

BarioSurg Inc. developed the *Gastric Vest System* (GVS), an implantable device that purportedly results in weight loss comparable to sleeve gastrectomy, but wraps around the stomach, and thus, leaves the stomach intact.

EnteroMedics acquired the GVS from BarioSurg and is now investigating ways to combine the GVS with its own vBloc technology, in clinical trials. GVS is undergoing clinical trials in Latin America, where it has shown more than 70% average EWL over six months and plans to conduct trials in the US.

BAROnova

BAROnova Inc., a startup in Goleta, California, hopes to win FDA approval with its TransPyloric Shuttle *weight loss system*. The device is placed into the stomach endoscopically and designed to self-position across the pylorus to create an intermittent obstruction to outflow and delay gastric emptying, resulting in early satiation and/or prolonged satiety or reduced hunger.

The device is currently being evaluated in a 270-patient study at nine US sites. The trial is expected to be completed in January 2018.

GI Dynamics

GI Dynamics Inc., based in Lexington, Massachusetts, developed the *EndoBarrier*, a thin and flexible liner that is transorally inserted and positioned just below the stomach into the GI tract to bypass a portion of the intestine.

It is designed to create a physical barrier between receptors in the intestinal wall and food being digested that releases gut hormone signals, resulting in increased satiety. The liner typically lasts for 12 months, then requires a second procedure to be removed.

The device is recommended for obese people with type 2 diabetes who aren't controlled well with medications and want to avoid surgery or intense injectable therapy.

The device gained the CE mark, but GI Dynamics reported that in May 2017, it was notified by the SGS United Kingdom Limited that the CE mark was suspended pending closure of "non-conformances related to its quality management system."

The company is working to correct the issue. It is also re-engaging contact with the FDA to seek approval for conducting a clinical study under an investigational device exemption in an effort to pursue FDA approval. This comes after GI Dynamics stopped an earlier clinical trial due to cases of hepatic abscess, all of which have been resolved.

GI Windows

GI Windows, based in Massachusetts, developed a unique magnet-based *incisionless anastomosis system (IAS)* whose mechanism of action is similar to bariatric surgery, which can result in durable weight loss and reduce co-morbidities from limiting the absorption of ingested fats and carbohydrates, and also due to changes in gut hormones triggered by bypassing ingested foods.

The company announced during Digestive Disease Week in 2016 that six-months results from a first human study of 10 obese patients with a mean BMI of 41, including four diabetic patients and three prediabetic subjects, showed significant reductions in HbA1c and fasting glucose levels. In patients with pre-diabetes, HbA1c levels were reduced from a mean baseline of 6.1% to 5.25% at six months and fasting blood glucose levels decreased from 119mg/dL to 105mg/dL; type 2 diabetics showed a decrease of HbA1c levels from a mean baseline of 7.8% to 6% at six months and fasting glucose falling from 177mg/dL to 111mg/dL. The mean weight loss for all patients was about 28lbs (12.9kg), representing a 10.6% total weight loss.

The company plans to present 12-month data in an upcoming publication and also use the data to submit for a CE mark in Europe this year.

Scientific Intake

Georgia-based startup **Scientific Intake Ltd.** has developed an affordable, totally noninvasive, oral, non-surgical retainer-like *SmartByte* device that has received the CE mark and in May 2017 a 510(k) approval as a Class II device from the FDA. The custom-molded, removable device is inserted on the upper palate during meals to help people eat more slowly and take small bites during eating and is removed when the person is finished with a meal. Doctors prescribe the device indicated for overweight and obese people with a BMI ranging from 27-35kg/m2, in conjunction with behavioral modification. Clinical trial results published in the medical journal Obesity showed that people have lowered their daily food intake by 23% (533 fewer calories a day) compared to people who didn't have the device in place. The company is marketing SmartByte to weight-loss clinics, endocrinologists, bariatric surgeons and cosmetic dermatologists.

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Chris Keeling | Tel: +44 (20) 337 73183 | Mobile: +44 (0) 7917 647 859
Email: christopher.keeling@informa.com
Headline Sponsor
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