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RELENTLESS RISE OF TRANSCATHETER TECH:

Heart-Valve Repair Turns Back On Open Surgery

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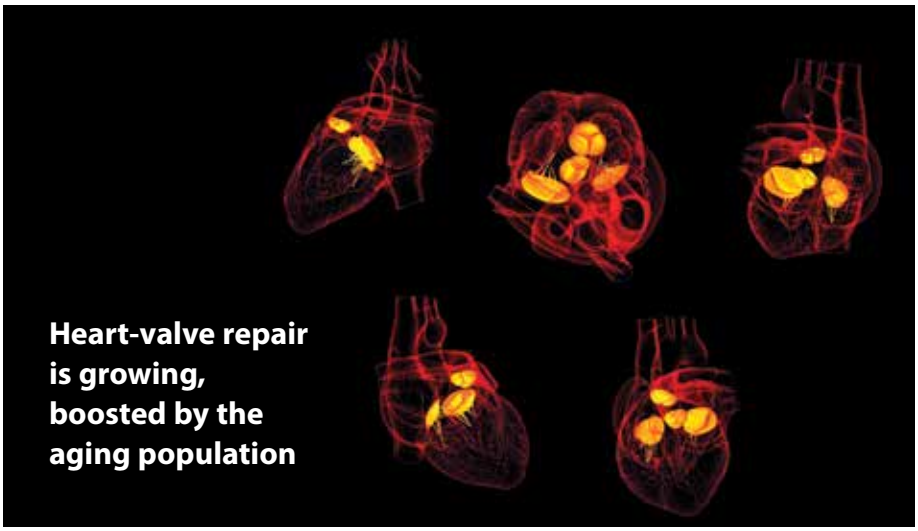
The global market for products treating heart-valve disease is forecast to grow from $4.8bn in 2016 to $8.1bn in 2021, at a compound annual growth rate (CAGR) of 10.9%. According to *Meddevicetracker*'s "Heart Valve Repair And Replacement Market" report, sales of traditional devices used in open heart-valve repair and replacement procedures accounted for about 41% of total product sales in 2016, as it gets overtaken by transcatheter technologies – a field currently dominated **Edwards Lifesciences Corp.**, **Medtronic PLC** and **St. Jude Medical Inc./Abbott Laboratories Inc.** – which held 59% of the total market.

By 2021, *Meddevicetracker* expects new technological advancements and continued expansion to a wider, younger patient population will significantly drive up market share of emerging transcatheter devices to 76% whereas the market share of invasive surgical procedures will drop even further to 24%.



Heart-valve repair is growing, boosted by the aging population

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TRANSCATHETER TECHNOLOGIES MARKET OVERVIEW

The *Meddevicetracker* report forecasts total worldwide transcatheter heart-valve-management product sales, comprising TAVR and TMVrep systems, to more than double from $2.85bn in 2016 to $6.2bn in 2021, representing a CAGR of 16.6%.

This is driven, in large part, by the growing numbers of valvular disease resulting from rising obesity rates and growing prevalence of diabetes worldwide. Another contributing factor is the growing evidence base supporting the benefits of transcatheter repair and replacement.

In 2016, more than 100,300 transcatheter heart-valve management procedures were performed globally, with the US and five major European countries – France, Germany, Italy, Spain and the United Kingdom – accounting for the majority of procedures performed.

Regional Perspective

Looking globally, *Meddevicetracker* expects that Japan will present the largest growth opportunity in this segment with sales rising by 66.8% from $31m in 2016 to a whopping $400m. Growth drivers include the rising elderly demographic, positive reimbursement and new device approvals. Edwards Lifesciences was the first company to win approval for its third-generation TAVR product, *Sapien 3*, in Japan last March.

The second biggest growth region for TAVR will be the emerging markets

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

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- **Mir Imran**, Founder, InCube Labs
- **James Mazzo**, Global President, Ophthalmic Devices for Carl Zeiss Meditec AG
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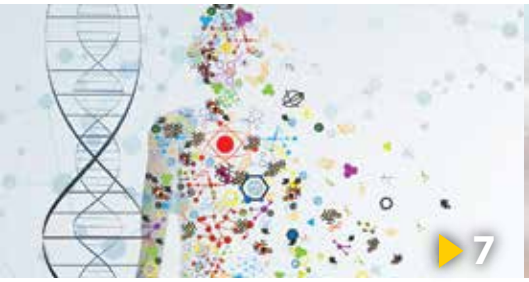

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SOFTWARE AT THE SPEED OF TRUST:

US FDA Launches Pilot To Expedite Digital Health Products

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Calling it a "once in a lifetime opportunity," FDA's top digital health official is encouraging companies to sign up for a pre-certification pilot that could allow them to get health software to market sooner and, in some cases, without filing a pre-market application.

After months of floating the idea to industry, FDA announced July 27 that companies can sign up for a pilot of the Digital Health Software Precertification Program ,or PreCert. The program will rely on FDA certifying and gaining trust in a firm's software-development practices. The agency says that the initiative, formerly referred to as the FDA Precheck program, could be a better way to address the rapid product development and constant updating that are hallmarks of digital health software. FDA acknowledges that its traditional medical device review pathways don't meet the sector's needs.

LISTEN

Hear our full interview with FDA digital health leader Bakul Patel online at http://bit.ly/2uUyhFV.

In an interview with *Medtech Insight*, Bakul Patel, FDA's associate director for digital health who spearheaded the idea, says the agency is conducting the pilot to help figure out what the full program should look like and what requirements need to be met.

Companies "who are able to validate design... and maintain software in a very, very good way that really keeps patients in the forefront, and are also proactive at the same time, are really what we are looking for," Patel said in the interview. Firms that meet that description can experience a "very streamlined" review premarket process, he said.

While the pilot program is set to start Sept. 1, Patel says the agency has decided not to set an application deadline; instead, companies can continue applying until FDA fills the nine slots. He says the agency wants to attract a diverse set companies to the pilot so they can scale the concept. even though they have limited it to only nine applicants they encourage companies to continue talking to FDA and giving them feedback.

"This is probably a once in a lifetime opportunity for us to work together collaboratively to make sure that the program is designed in a way that actually helps not only the industry but also more importantly the patients that we all care about and we want to get the highest quality technology to the patients in the US," said Patel.

FDA has scheduled a webinar on Aug. 1, to provide more information about the pilot program and will hold a public workshop in January 2018 to report its initial findings.

LOWERING REGULATORY BARRIERS

FDA Commissioner Scott Gottlieb, announced the pilot program as part of FDA's overall Digital Health Innovation Action Plan in a blog post.

"The challenge FDA faced in the past is determining how to best regulate these non-traditional medical tools with the traditional approach to medical product review. We envision and seek to develop through the Pre-Cert for Software Pilot a new and pragmatic approach to digital health technology," he said. "Our method must recognize the unique characteristics of digital health products and the marketplace for these tools, so we can continue to promote innovation of high-quality, safe, and effective digital health devices."

Companies interested in participating in the pilot program can do so starting August 1 and must meet all three requirements laid out by FDA. Specifically:

- The company is developing or plans to develop a digital health software product;
- It has an existing track record of producing software based on a culture of quality, measured by Key Performance Indicators (KPIs); and
- It agrees to give the agency access to those KPIs, as well as provide FDA with real-time and real-world data and communication about its product and provide information about its quality management system.

Earlier this summer Gottlieb used FDA' blog to outline his vision for implementing software provisions in the 21st Century Cures Act and removing regulatory ambiguity that that included among other ideas the plan to implement a precertification program. *(Also see "US FDA's New Game Plan For Digital Health" - Medtech Insight, 15 Jun, 2017.)*

At that time, the agency stated it was garnering industry feedback and for the most part had received positive responses from stakeholders. *(Also see "US FDA Collecting Feedback On Digital Health Plan" - Medtech Insight, 16 Jun, 2017.)*

Earlier this year, Patel also floated the precertification program idea to industry stakeholders at the AdvaMed Digital Medtech Conference in San Francisco, though he called it an FDA Precheck program, referencing the "Precheck" system used to expedite plane entry at airports. He asked stakeholders for advice on what ideally such a program should look like. *(Also see "FDA Pitches Novel Pathway For Software" - Medtech Insight, 9 Mar, 2017.)*

Industry stakeholders had a positive initial response to the July 27 announcement and the speed at which the agency appears to be moving in streamlining regulation of digital health. "It's rather unbelievable how fast FDA is moving in a positive direction," said Bradley Thompson, who represents the industry Clinical Decision Support coalition.

OPPORTUNITY FOR NON-TRADITIONAL MEDTECH

As non-traditional medical device companies have entered the market who specialize in software and more generic digital technology, the potential to develop "software as a medical device" has grown, but has also raised questions about the tenability of

traditional device review pathways to evaluate such products

Patel says the precertification program may create incentive for such non-traditional companies to enter the market and develop new digital health software products.

"We think digital health can bring lots of benefits to patients," he said. "Many software companies who are probably now not making medical device software may now be interested in making medical device software. The fact is we are seeing this excitement and the potential for the software to actually provide a unique promise that it holds for patients."

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Health-Care Bill Failure Triggers Renewed Search For Device Tax Repeal Option

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A failed last-ditch effort in the Senate by Leader Mitch McConnell, R-Kent., to get his party to accept a "skinny repeal" version of a GOP health care bill early on July 28 could also spell the end of industry's chances to win a device tax repeal or delay this year – unless they can find another legislative vehicle.

But the at least temporary pause in the Senate's focus on health-care reform provides the opportunity for another industry-favored bill – the FDA Reauthorization Act (FDARA) user-fee legislation – to finally come to the chamber's floor for passage.

The "skinny repeal" bill, known as the Health Care Freedom Act, was a slimmed-down version of previous Affordable Care Act repeal measures, and would have delayed the 2.3% device excise tax until Dec. 31, 2020. But it went down in flames, along with near-term GOP efforts to repeal Obamacare, after Republican Sens. John McCain, Ariz., Lisa Murkowski, Alaska, and Susan Collins, Maine, voted "no" along with all Senate Democrats.

In addition to delaying the device tax for another three years, HCFA would have ended the individual and employer mandate to purchase insurance, let individuals with health savings accounts contribute more dollars to them for three years, delayed Medicaid reimbursement of Planned Parenthood expenses for one year, and eliminated the Prevention and Public Health Fund in 2019.

The Senate adjourned for the weekend after the skinny repeal vote failed. It's unclear whether there will be any more health-care reform efforts this year. Interest groups including health insurers and the American Medical Association say they hope that Republicans will regroup and try to work out a compromise measure with Democrats that will make some fixes to the ACA without throwing too many Americans off insurance rolls.

In the meantime, device groups including AdvaMed may need to step up ongoing efforts to find another vehicle for repeal, or at least an extended delay, of the excise tax. Talk of FDARA as a possible device-tax repeal vehicle has ramped up in recent days. The bill has broad support in Congress; it has already passed the House, but has been held up in the Senate due to the focus on health-care reform. Adding device-tax repeal, however, would potentially complicate a non-controversial bill by adding more cost to FDARA and requiring a new vote in the House. The user-fee reauthorization must be enacted by the end of September, when the current user-fee programs expire. *(Also see "Capitol Hill Update: Congress Gets Reprieve On User Fee Passage, While AdvaMed Weighs Device Tax Options" - Medtech Insight, 26 Jul, 2017.)*

Other options on the table are a Children's Health Insurance Program (CHIP) reauthorization bill or a budget bill.

The trade group is seeking "the fastest way to device tax repeal attached to any vehicle," a spokesman said July 26.

"The medtech industry stands ready to work with lawmakers on both sides of the aisle to avoid a looming, billion-dollar tax increase on American manufacturers," AdvaMed President and CEO Scott Whitaker said July 28 in a statement provided to *Medtech Insight*. Whitaker also offered "special thanks" to senators who have worked to repeal the tax.

"The medical device tax is a proven jobs-killer," Whitaker said. "A deadline remains, so we want to work with Congress to act quickly and end this tax for good."

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EMA Plans Guidance To 'Closely Knit' Development Of Companion Diagnostics And Drugs

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The European Medicines Agency is inviting feedback on its proposal for a guideline to address the challenges related to developing personalized medicines with companion diagnostics (CDx). A draft version of the guideline is expected to be available for consultation by the middle of next year.

The EMA's guideline proposal is outlined in a concept paper, which explains that, at present, the development of medicinal products and the *in vitro* diagnostics that are used to assess which patients would most likely to respond to the drugs is often independent, "coming together only superficially towards the end." This is not ideal as gaps can remain in evidence and validations. The proposed guideline will offer recommendations on using a close-knit development program linking the two, and on the use of clinical trials to generate evidence required to support validation of the diagnostic.

Specifically, the guideline will provide recommendations relating to the interface between predictive biomarker-based assays, including CDx, and the development and lifecycle of medicinal products. When finalized, it is intended to help companies comply with the new EU In Vitro Diagnostics Regulation (IVDR), which envisions cooperation between medical device notified bodies and drug regulators to evaluate new companion diagnostics for a CE mark. *(Also see "Officially Here: EU Medical Devices And IVD Regulations Are Published" - Medtech Insight, 5 May, 2017.)*

Is important to clarify how evidence to support the validation of a companion diagnostic can be generated during the development of a medicine, the EMA believes. The guideline will address situations where a CE-marked IVD might not be available to measure potentially predictive biomarkers, especially novel biomarkers, during drug development. In such cases, the assay used in clinical development may itself be eventually co-developed as a CDx. The guideline will discuss the potential to align technical assay validation and clinical evidence requirements for drug approval with technical and clinical performance requirements for CE marking.

New EMA guidance will address development challenges for personalized medicine

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To facilitate the development of suitable tests for use in the clinic, the guideline will discuss concordance testing and bridging studies, including testing of stored patient samples. The interchangeability of assays that have been co-developed with more than one drug, but measure the same predictive biomarker, will also be considered. The impact of potentially non-harmonized life cycles of medicinal products and CDx including medicinal product labelling variations (e.g., new indications or patient populations) and test assay modifications will be considered.

The guideline will also define and explain the regulators' understanding of specific terms in a glossary, such as analytical/clinical validation/performance, clinical utility, concordance studies and training, and validation sets.

The development of the guideline will be led by the EMA's Pharmacogenomics Working Party and will also involve other working parties, including the Scientific Advice Working Party, the Oncology Working Party, the Biostatistics Working Party as necessary, as well as the European Commission's IVD working group.

Comments on the EMA's concept paper will be accepted until Oct. 31, 2017. When finalized, the concept paper will replace the agency's 2010 reflection paper on co-development of pharmacogenomics markers and assays in the context of drug development.

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UK's NICE Updates Policy For Preventing Bias In Advisors

UK health technology assessment (HTA) body NICE is seeking comments on planned changes to its conflicts of interest policy for ensuring that the decisions its advisory committee members make are fair and unbiased.

The new draft policy provides more explicit guidance and clarification on declaring and managing conflicts of interest for advisory committee members compared with the three-year-old policy it will eventually replace, says NICE (National Institute for Health and Care Excellence**)**. It also explains how NICE handles any conflicts.

The update was prompted by guidance from the National Health Service on managing conflicts of interest that was published earlier this year. "We are aligning our policy to reflect the environment in which we work, i.e., the NHS," a spokesperson for NICE told *Medtech Insight*.

Committee members and advisers bring a range of experiences and perspectives to the work NICE does, the HTA body said. This is likely to mean they will have a variety of different interests, arising from different contexts and from activities undertaken in a professional or personal capacity. "We need to make sure that members of committees declare relevant interests so that any possible competing interests or risks of bias can be identified," said NICE's deputy chief executive, Gillian Leng. **"**This is an essential part of our process to develop robust guidance of the highest quality."

The draft policy says that all interests should be declared if, in the view of a reasonable person, they are relevant, or could be perceived to be relevant, to NICE's work,

The policy provides a clearer distinction between interests that should be declared and those interests which are declared and are a conflict of interest. "It talks about the difference between direct and indirect interests," the NICE spokesperson said. "For example, interests that are declared can be an indirect interest but would not be a conflict of interest." The section in the policy on "identifying and responding to potential conflicts of interest" details when declared interests are a conflict of interest.

> "We need to make sure that members of committees declare relevant interests so that any possible competing interests or risks of bias can be identified" – NICE deputy chief executive Gillian Leng

The new policy clarifies that only interests that are relevant or potentially relevant to the work of NICE need to be declared. It provides more explicit guidance on when an interest is specific to the matters under discussion and therefore gives rise to greater risk of a conflict of interest. Specific interests, it explains, are those that relate to matters under consideration at a particular committee meeting, and these interests are where conflicts are most likely to arise. Specific interests include anything that relates to, or informs, a potential recommendation, including all:

- products and competitor products;
- interventions, including public health interventions and diagnostic tests;
- topic areas, such as diagnosis or investigation of clinical issues; and
- underpinning research papers or economic analyses.

Specific interests do not include having a general interest in the topic under discussion, such as the provision of social care, or pharmacy or laboratory services, through being a salaried employee in a commercial organisation that provides these services.

There is also more explicit guidance on when private practice and other fee-paid work should be declared and the impact on an individual's involvement in guidance development.

The new policy clarifies that there are three potential responses following a declaration of interest:

- no action other than the process of open declaration – the individual can engage in all aspects of the committee's work;
- partial exclusion – the individual can engage in committee discussion or provide advice to the meeting, but is excluded from developing recommendations and decision-making on the matter relating to the interest; or
- complete exclusion – the individual can have no input to a specific topic, either from the very start (non-appointment) or for part of the committee's work in relation to that topic.

There are examples at the end of the policy that outline hypothetical examples of committee members declaring conflict of interests and what to do with them.

Comments on the new policy must be submitted by Sept.18. "In particular, we would like to hear if the draft policy is clear and understandable, and whether it will ensure the right level of expert input, whilst ensuring confidence in the integrity and objectivity," Leng said. The comments will then be considered by the NICE board, with a view to implementing the new policy in early 2018.

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German Electromed Industry View Of Brexit: We Can Cope

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The health-care branch of German electro-industry association ZVEI (Frankfurt) has polled its members on the possible forthcoming effects of Brexit and found that the UK's exit from the EU in two years (if things go precisely to plan) will make some – but not much – difference to the business of German electromedical industry manufacturers.

Not all ZVEI members responded to the survey, but there was enough feedback to give a sound impression of views. Most replied that the UK *is* a market for them, but it's not the most important one. The sense conveyed was that "we are selling in the UK but it's not the bulk of our business." Only a few German electromedical companies have manufacturing sites in the UK. Deliveries from the UK to Germany are rated as being of low importance.

In summary, the majority of German electromedical technology manufacturers expect no serious short-term effects from Brexit. The German market for electromedical equipment is set to grow by 5% in both 2017 and 2018, ZVEI believes. German capital equipment sales are flat, but consumables are growing in line with patient demand and the aging population. (see box *Global Electromed Market Drivers*).

CUSTOM UNION, NB CONTINUITY, POTENTIAL MDR ISSUES FOR UK

There are concerns, however, about what trade deals can be hammered out with the UK. EU Brexit negotiator Michel Barnier is firm that "outstanding bills" and accounts must be settled and EU citizens' rights guaranteed (by the European Court of Justice if needs be) before trade agreements can be broached. UK Brexit negotiator-in-chief David Davis has already been rebuffed on these issues, and will surely continue to be. *(Also see "Brexit Health Alliance Adds To UK-EU Debate; Medtechs Settle Into Interim Brexit Pace" - Medtech Insight, 20 Jul, 2017.)*

On the contrary, seemingly well prepared for all eventualities, ZVEI members have looked into any supply problems that could arise from the UK's EU exit, and most say that those they have identified are not critical or important, the head of ZVEI's health-care branch, Hans-Peter Bursig tells *Medtech Insight*. Most companies have replied that they would be able to find alternative supplies/suppliers to resolve problems in individual cases.

But Bursig observes that, although the UK is currently ruling out membership of the single market, its exit from the customs union would be even more damaging and could, in fact, have a big impact on manufacturers' supply and value chains. He also voices concern over the continued applicability of the CE-marking in the UK, and the doubtless more worrisome issue of UK notified body input into EU regulatory and auditing operations in general.

The UK will sweep existing EU law into UK law, as explained recently by FieldFisher legal expert Alison Dennis. *(Also see "UK Medtech One Year Post-Brexit Vote: Still In The Land of Uncertainty" - Medtech Insight, 4 Jul, 2017.)* But the timing of the EU Medical Device Regulation coming into practice (May 2020, which would come after Brexit, if all goes to plan) and the specter of the ECJ acting as the legal arbiter in future disputes under the twin MDR and IVDR regulations (unacceptable to UK Brexit negotiators) could unleash a host of medtech regulatory compliance complications in the UK.

Also, if the UK steps out of line with EU environmental regulation, UK medtech suppliers may no longer be viewed by their EU counterparts as a consistent source of reliable supply.

Global Electromed Market Drivers

The global electromedical market in the near term will be driven not by Europe but by Asia and the Americas, which both grew by 7% in 2016, with 7-8% market growth forecast for both in 2017 and 2018. Europe is the global laggard, expanding by just 3% in 2016, and the same is expected in both 2017 and 2018. That is according to the electromedical branch of Germany's ZVEI electro-industry association, from its own estimate of a 2015 market valued at €95.4bn ($111.6bn). The US is the biggest market, at €37.6bn.

The sector's competitive aspect should guarantee that innovation flows at continuous high levels, but MNCs and SMEs alike have a new challenge – the digitization of health-care and medtech – which is rapidly gaining currency and being given context by government initiatives such the German health ministry's new digital health dialogue platform. The platform aims to bring together stakeholders in health-care, the economy, and science to work out how best to use big data, and to identify appropriate medical technology needs, while factoring in cybersecurity requirements.

WISE TO KICK THE BEEHIVE?

In kicking the EU beehive, UK Brexiteers have yet to see to see the extent and duration of the impact of their chosen course on local medtech businesses. Their German electromedical counterparts are a step ahead. Their typical reaction right now is, *We'll adjust; we can live with that*. The current strength of the Euro, at almost $1.17 and seemingly heading for $1.20, might complicate matters further, of course.

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Tighter Australian Rules Spell More Work For Surgical Mesh And Other Implant Makers

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Australian medical device regulations are being aligned with the new EU rules

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Australian regulators are seeking comments on proposals to up-classify surgical meshes and introduce formal requirements for companies that make these and many other types of implants to provide patients with medical device ID cards.

Both actions are part of plans by the Therapeutic Goods Administration to align its medical device regulations, where possible, with the new EU Medical Device Regulation that was published in May.

Under the proposals, which were released for consultation on July 28, all implantable surgical meshes would be reclassified from class IIb (medium-to-high risk) to class III (high risk). In addition, manufacturers of mesh devices and other types of implants, such as orthopedics devices and active implantable devices, would have to provide consumers with patient implant cards and product information.

The proposals will mean extra work for companies. For example, the up-classification would require surgical mesh manufacturers to seek additional conformity assessment certification. "Manufacturers will already hold certification of full quality assurance procedures, but will now also require design examination certification for each mesh medical device," the TGA said. Sponsors of existing surgical mesh devices already included in the Australian Register of Therapeutic Goods as a class IIb product will need to apply to have their device/s included as class III medical devices, the agency added.

The proposal to formalize the requirement for implant cards and patient information leaflets would apply to all implantable devices and long-term surgically invasive implants (i.e., all class IIb, class III and active implantable medical devices, except certain products such as sutures, staples and dental fillings, among others in a similar category).

While Australian regulations currently require manufacturers to provide certain information with their devices, the proposed change would make the requirement for patient cards and information explicit in the regulations, with the goals of improving information flow to patients and doctors and improving patient-doctor discussions.

The requirement aligns with the new EU regulation, the TGA said, noting that under Article 18 of the MDR, for example, implant makers must provide together with their device "information allowing the identification of the device, including the device name, serial number, lot number, the Unique Device Identifier (UDI), the device model, as well as the name, address and the website of the manufacturer."

Sponsors relying on European certification for their relevant ARTG entries would be required to submit a manufacturers' evidence update to demonstrate compliance with the change.

There will be a transition period for both the up-classification requirement and the patient implant card rule that mirror the three-year transition period in the MDR.

The deadline for submitting feedback to the TGA's consultation is Aug. 25.

FURTHER ALIGNMENT WITH EU RULES PLANNED

The TGA's latest proposals follow the government's September 2016 response to the Medicines and Medical Devices Regulation (MMDR) review on how to reform and enhance Australia's regulatory framework for health care products.

The agency said it was planning to consult on other measures to further align the country's device regulation with Europe's new MDR in 2018. TGA said started with the up-classification and device ID measures because of their "ability to positively impact on patient safety around mesh devices."

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SNAPSHOT: US Pediatric Device Approvals Stay Steady, Despite Overall FDA Surge

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A recent surge in novel device approvals by US FDA did not include a proportionate spike in new devices with pediatric indications, according to recently released data from the agency.

FDA must send a report annually to Congress detailing devices approved with pediatric indications. The latest report, posted July 26, includes data through FY 2015, which was a record-setting year overall for original PMA approvals. *(Also see "FDA Hits User-Fee-Era Record For 'Novel' Devices: A New Normal?" - Medtech Insight, 14 Jan, 2016.)* The total number of original PMAs, panel-track PMA supplements and humanitarian device exemptions approved in FY 2015 was 61, a 65% increase from the 37 such approvals in FY 2014.

But the number of device approvals in those categories that included patients 21 or younger in the product labelling increased by only 38%, from eight to 11 approvals, according to FDA's latest report. The 18% of devices that included pediatric indications in FY 2015 was the lowest proportion since FY 2009. The peak proportion was in FY 2010, when eight of 20 (40%) PMA, panel-track supplement and HDE approvals including 21-or-under patients. The most pediatric-including indications approved in recent years was the 15 approved FY 2011.

Of the 11 approvals in FY 2018, several had indications targeting patients 18 years of age and older, while other sent down to ages 12 or 13. There were several that listed an indication for "pediatric or adult" patients more generally. Only approval was exclusive for pediatrics, **Dexcom Inc.**'s May 2015 PMA supplement approval for the pediatric version of its *G4 Platinum continuous glucose monitor* for 2- to 17-year-olds. Also, **Roche**'s *Elecyc Anti-HCV II Immunoassay* was PMA approved June 2015 specifically for patients aged 18 months to 21 years, although the approvals also included a control reagent for use in all ages.

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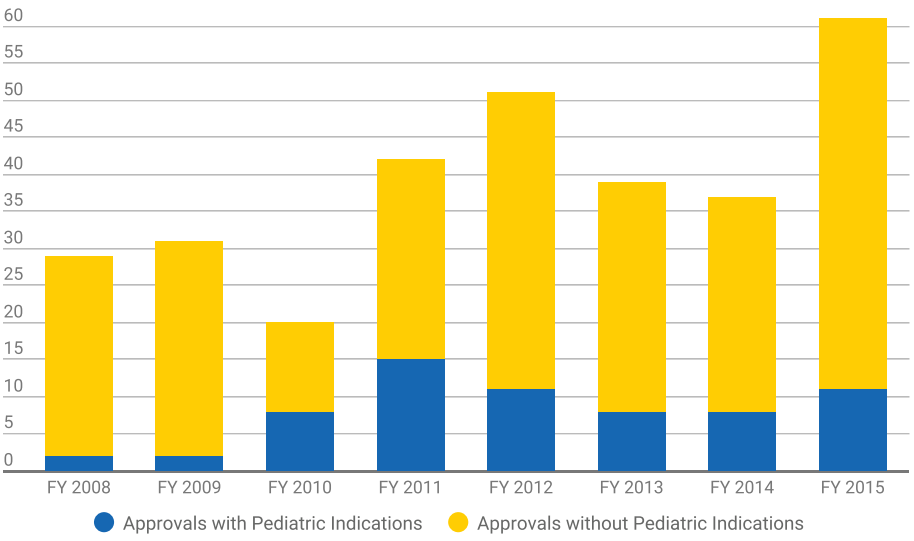
Pediatric-Including Vs. Non-Pediatric PMA, Panel-Track Supplement and HDE Approvals, FY 2008-2015



Source: FDA

Increasing development of devices studied in or designed for younger patients has been identified as a priority goal by policymakers and industry in response to lack of availability of products for children and the need in some cases for clinicians to find ways to use devices designed for adults on kids. Congress has established mandates to report pediatric applications, award grants focused pediatric device development and loosen profitability restrictions for HDE devices, among other reforms, to try to address the issue. *(Also see "FDA Focusing On Promotion Of Pediatric Device Development In 2014" - Medtech Insight, 13 Jan, 2014.)*

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US FDA's Device-Focused Patient Engagement AdComm Tackles Trial Challenges

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Two years after its launch, US FDA's device center will convene the first meeting of its Patient Engagement Advisory Committee in October to discuss patient perspectives in clinical trials.

On July 25, CDRH Director Jeff Shuren and Kathryn O'Callaghan, assistant director for strategic programs at the center announced the first meeting of the Patient Engagement Advisory Committee, or PEAC, in an agency blog post. According to the FDA officials the group of nine committee members will meet for the first time on Oct. 11-12 in Gaithersburg, Md. to discuss challenges of clinical trial design, conduct, and reporting identified by patients. The meeting will come about two years since the device center first announced the launch of PEAC. *(Also see "FDA Launches Patient Engagement Advisory Committee For Devices" - Medtech Insight, 22 Sep, 2015.)*

"FDA chose this subject because patients often have concerns about participating in clinical trials or drop out once they have enrolled in a trial," Shuren and O'Callaghan wrote. "Inconsistent or minimal participation in clinical trials can make it difficult to reach reliable conclusions or to determine the level of benefit for patients. It also can take longer to bring technological advances to the patients who need them."

In general, FDA is calling the committee "a forum for the voice of patients" who will be asked to advise the agency on medical device issues and their impact on patients.

"The goal of PEAC is to better understand and integrate patient perspectives into our oversight, to improve communications with patients about benefits, risks, and clinical outcomes related to medical devices, and to identify new approaches, unforeseen risks or barriers, and unintended consequences from the use of medical devices," the officials said.

FDA also states it needs better tools to capture and characterize patient views to maintain an acceptable balance between benefits and risks. The authors also added they need to adapt their policies to evolving science in patient preference.

The device center has been working to incorporate patient preference into its regulatory decision-making process for about the past five years. *(Also see "FDA Validates Tool For Incorporating Patient Preferences In Regulatory Decisions" - Medtech Insight, 30 Sep, 2013.)* FDA has worked with groups such as the Medical Device Innovation Consortium (MDIC) and Duke University's Margolis Center for Health Policy to develop new statistical methods and means to incorporate patient views into decision-making.

In January 2015, FDA approved **EnteroMedics Inc.**'s *Maestro Rechargeable System*, a pacemaker-like device used to help obese patients control hunger cravings. It was first device explicitly approved by the agency based on patient preference data. Since then, the agency has been working in close collaboration with MDIC on the issue, leading to a final guidance issued last year on using patient preference in medical device applications. *(Also see "Final Guidance Encourages Use Of Patient Preference In Device Applications" - Medtech Insight, 25 Aug, 2016.)*

While MDIC says it was not involved in the advisory committee, it supports the initiative and looks forward to interacting with them.

MDIC President Bill Murray says he's happy the agency has chosen clinical trials as the first topic the committee will tackle. He points out MDIC has been working with CDRH, the Massachusetts Institute of Technology, RTI Health Solutions and The Michael J. Fox Foundation for Parkinson's Research on a project to integrate patient preferences into the statistical endpoints of clinical trials. *(Also see "MDIC Project Looks To New P-Value Possibilities" - Medtech Insight, 20 Oct, 2016.)*

"We are working on a proposal to build on that project to develop a framework for patient input in clinical trials," he added. "Patient input in clinical trials is critical and we are pleased that CDRH has encouraged this committee to explore how patients might be able to help medical device companies think about how they can better solicit and integrate patient input into the design of their clinical trials."

Murray says the creation of the new advisory committee on top of the 50 advisory committees FDA already relies on is an extension of the agency's work delving into patient preference.

PEAC Roster

- Paul T. Conway (Chair), president of the American Association of Kidney Patients
- Katherine Seelman (Consumer Representative), Retired professor of rehabilitation science and technology, University of Pittsburgh
- Cynthia L. Chauhan, patient advocate and retired social worker
- Bennet R. Dunlap, consultant and diabetes advocate
- Frederick Downs, Jr., retired Veterans Administration procurement and logistics officer; decorated Vietnam veteran
- Amye Leong, president and CEO of Health Motivations
- Monica Willis-Parker, director of the Minority Engagement Core, Emory Alzheimer's Disease Research Center.
- Deborah Cornwall, patient advocacy expert
- Suzanne Schrandt, director of Patient Engagement at the Arthritis Foundation; previously a deputy director at the Patient-Centered Outcomes Research Institute (PCORI)

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US Supreme Court Case Could End Patent Office Re-Examination Procedure

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A US Supreme Court decision expected this fall could undo recent changes to the patent review system that have sometimes been a thorn in the side of patent holders in the medical technology arena.

The Supreme Court recently agreed to hear a case, *Oil States Energy Services LLC v. Greene's Energy Group LLC*, that questions whether the patent review procedures established via the 2012 America Invents Act (AIA) are constitutional. The plaintiff says the patent office courts violate a constitutional ban on taking away property without a jury trial.

While the ruling would apply to all industries, it has special relevance to innovation-driven industries such as the medical device field.

The AIA allows any petitioner to file a challenge with the patent office asking for a patent to be re-examined. Usually, the argument is that the patent is invalid, either because the idea was unpatentable or because prior art means the patent shouldn't have been issued. Administrative judges employed by the US Patent & Trademark Office (PTO) review the challenged patents in a process known as *inter partes* review, or IPR.

Patent owners in the life-sciences space – drug companies in particular, but also some device firms – have complained that the IPR process made them too vulnerable to challenges from not only potential competitors but hedge-fund managers or other parties looking to impact a company's stock with a potential challenge, though some changes have been made to address the concerns. *(Also see "Patent Office Revising PTO Challenge Proceedings" - Medtech Insight, 6 Apr, 2015.)* On the other hand, the process provides a more accessible route for companies to enter a market that might be blocked by questionable patents.

IPR proceedings take around 18 months and cost $35,000, plus attorney fees that can rise to the six figures, says Brent Babcock, a patent attorney with Knobbe Martens who has clients in the device and drug industries, among others. "About half of the challenged patents are cancelled," he said. "This is very instrumental in weeding out patents. There have been several thousand of these proceedings."

There's no question Congress wanted to establish a procedure like IPRs as part of an effort to discourage patent trolls and other bad patents, Babcock said in an interview. In addition, the patent office has performed similar re-examinations on request for decades.

But *Oil State* could bring the procedure screeching to a halt, Babcock says. PTO judges are not appointed by the US President or approved by the Senate, and the challenge process doesn't include juries. "The fundamental question here is, does allowing the patent office to take away your patents violate the Seventh amendment requirement that before the deprivation of life, liberty or property, you be heard by a jury?" he says.

A party challenging a patent in court before an appointed judge would have the option of a jury trial under the Seventh amendment to the US Constitution. Jury trials can favor patent-holders because jurors are traditionally reluctant to invalidate patents, Babcock says, adding "[patent invalidation] happens, but it's not as common as in front of the IPR board."

The government's counter-argument, he says, is, "This is what administrative offices do; they review things that they've granted." And he believes that challenging the patent office's review rights under administrative law could have repercussions for other agencies that use an administrative review process, such as FDA. However, the plaintiff has argued its case is unique because patents represent property.

If the Supreme Court takes the most drastic action suggested by the plaintiff, the IPR process would be immediately

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declared unconstitutional. But it's far from clear what might happen retroactively to patents that have been cancelled during the past five years. Excluding patents that have already been through the IPR process might limit confusion, but Babcock believes that ruling could lead to more lawsuits. "People who have lost patents would feel it was pretty unfair if they lost a patent through a method that was later determined unconstitutional," he points out.

Eliminating IPR might also encourage companies to be less cautious about patent filings, he says. Right now, companies are selecting what to file on carefully because of the increased risk the patent might be ruled invalid.

This is the third time the Supreme Court has been asked to rule on the issue. Babcock says the outcome is unpredictable, but he expects the court to ultimately uphold IPRs and administrative review. "I focus on the practical issues, which is what would happen to the whole system if the Supreme Court threw it out," he said. "It would be a mess, and I don't see how the court could ever do that because of the terrible repercussions."

The Supreme Court's decision in the case is due by Nov. 20.

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Illumina Enters Second Wave Of Growth As Genomics Demand Swells

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It was just over five years ago that **Illumina Inc.** was fending off a hostile takeover from diagnostics heavyweight **Roche**. At that time, Roche's offer of $44.50 per share to buy the genomic analysis technology specialist represented what seemed like a generous premium over Illumina's stock price then, which hovered roughly around the $30 mark before rumors of the acquisition bid started inflating the value.

Illumina held its ground and turned its back on the Swiss group – not without some push back from some of its shareholders – stating in blunt terms that the offer was "grossly inadequate in multiple respects" and "dramatically undervalues Illumina." (*Also see "Roche refuses to budge on price in face of snub from Illumina board" - Medtech Insight, 8 Feb, 2012.*) (*Also see "Illumina sued by shareholders for Roche rebuff" - Medtech Insight, 16 Feb, 2012.*)

Snubbing Roche proved to be an astute move. Five years on and Illumina's share price has soared over $100, boasting a range of $160.10-173.52 in the first six months of 2017. Its top-line has more than doubled, from just over $1bn in fiscal 2011 to nearly $2.4bn in fiscal 2016. On Aug 1, the firm will announce its second-quarter 2017 results, and revenue for that period is expected to grow – based on the averaged estimates from 17 analysts – some 7% year-over-year to around $642m, while the outlook for fiscal 2017 is estimated growth of 10% to around $2.65bn.

The rise of Illumina reflects the escalation of genomic medicine over these past few years, boosting the demand for gene-sequencing and analysis solutions that can provide more tailored, personalized health care. The firm has carved itself a position as one of the leading go-to provider of these tools in both the life sciences research space and increasingly the clinical and health care sector. In February 2016, Illumina announced a partnership with Genomics England in which the US firm will develop interpretation and reporting tools for delivering reports on all genomes that are sequenced through the 100,000 Genomes Project. Genomics England will provide access to whole genome sequence and de-identified phenotypic data for the development of this suite of tools for personalized medicine. The tools will be used to curate and manage the knowledge base of information generated over the course of the project with a focus on rare disease and common cancers. The two parties solidified their alliance last month when Genomics England appointed Illumina as the primary vendor of variant interpretation and reporting software for tumor and matched normal samples characterized as part of the 100,000 Genomes Project.

Paula Dowdy, Illumina's Senior VP and General Manager, Commercial Operations for EMEA

Photo credit: Illumina

The genomics wave within health care will continue to swell even more, believes Paula Dowdy, Illumina's Senior Vice President and General Manager of Commercial Operations for EMEA.

Dowdy was appointed to this role exactly this time a year ago, bringing with her over 20 years of experience working for IT and networking leader Cisco. There, she held a number of senior positions leading the firm's product and services groups, and her last role before going to Illumina was Senior Vice President for Cloud, Software, and Managed Services at the tech company. "When I joined Cisco in 1996, it was prior to the internet boom and it was a phenomenal time to join the industry, right as it was taking off and growing through that internet phase. Cisco was already a successful company but the take-up of how important the internet, IP networking, the globalization of data, a voice of everything – all that was not known then," she told *Medtech Insight*.

While Dowdy did not have a background in life sciences, what intrigued her about the opportunity to be part of Illumina was that the company is now at the same juncture in the genomics revolution as Cisco was in the internet revolution when she joined it in the late 90s. "Cisco's objectives were to change the way we worked, lived and played around the internet, and Illumina is seeking to really impact human health care with its technology, with its vision, with whole genome sequencing."

Drawing further parallels between the tech and genomics industries, Dowdy added that Cisco already had its first big wave of growth with the introduction of the router in the early 1990s, and it was at the cusp of its second wave of growth as a networking company when she joined.

Likewise, Illumina has already had its first wave of growth just based on strength of its gene-sequencing and analysis technologies, enabling it to build itself to a $2bn-plus-revenue company it is today. "Now we are at that next phase, moving from a predominantly life sciences research-oriented company to a clinical and healthcare company," she said. "It's interesting when you look at businesses: what got you through wave one won't necessarily get you through wave two, and so the type of leaders you need in the company will change. In wave one, you are focused on the technology, the technology will sell itself and it matters a little less around commercialization and your capability around go-to-market. But in wave two, you are starting to think much more about creating markets.

"It took some time for me to get my head around moving industries but it was clear that [joining Illumina at this point of its growth], I could bring not just leadership experience but also business experience – working across multiple functions, seeing transitions of markets, seeing transitions of ways you go to market, through direct and indirect channels." Additionally, having worked as an American in Europe for a long time, Dowdy felt she was able to bring that translation of what needed to be done differently for a US-based company to be successful in Europe.

In the Q&A below, Dowdy provides an insight into Illumina's strategies for growing its commercial operations in Europe, what she feels the past year's key achievements have been, what are the changing needs of Illumina's customers and how that is driving the company's evolution and growth in coming years.

Medtech Insight: What immediate tasks were you charged with when you joined Illumina a year ago?

Paula Dowdy: Illumina clearly was a very successful company [when I joined] but like many US-based tech companies, it was somewhat dependent on US leadership. So, bringing a more local leadership structure across the different functions was absolutely paramount.

One of the things to be mindful of is that our CEO Francis deSouza [*who was President before assuming the additional role of CEO in July 2016, succeeding Jay Flatley who remains chairman- Ed*] had a number of strategies: one was to be more global, two to be more digital, three to be more clinical. I know he also has had a talent strategy where he believes there are certain roles where you can go out of the life sciences sector to get the best in breed; whether that be in commercial, supply chain, IT. Clearly our R&D functions need to have the best and brightest scientists in our industry but there are other areas where we can take advantage of background, experience and ability to scale businesses.

In the past year, what do you feel has been your biggest achievement at Illumina?

First and foremost, I'm really proud that we have created a cohesive leadership team. The inner play of business functions between sales, marketing, services, strategy, PR, operations – I lead Europe and therefore like any company, big or small, you have limited resources, so for us, right now, we need to be more thoughtful about where our business is going to come from in the future. Placing our resources on our priorities and focus and then executing against that has been critical.

Sales and marketing is arguably becoming more a science than an art, and for us, it's about being much more intelligent about what our customers of the future want from us. Not just from a technology perspective but also an engagement and experience perspective. This is absolutely paramount, but also really challenging for the organization to operate at a higher level.

Also, we are now looking to a longer-term horizon. We're starting to build a three-year business plan versus a one-year business plan and looking at where our future is and where our growth is going to come from; who the customers in our various markets are and who are the leaders in those spaces and how we can help facilitate their success and be a benchmark for others to follow.

It's about running it like a business, starting to have different measures and mechanisms in place. As a start-up company, the only focus will be on revenue but Illumina now has an extensive balance score card, which looks at how we are developing our pipeline, how our customers are responding to our service and support, how we are adopting e-commerce, and what the feedbacks on our marketing programs are. So it's taking it to a level of sophistication where we can measure the impact of the investments we are making in the European market.

As an American leading the EMEA operations of a US-based company, have you encountered any challenges specific to the geographic markets that you're responsible for?

I think it's both challenge and an opportunity. Europe is not one place, it's lots of countries. Then you add Middle East and Africa and it's many more countries. Our business here will have lots of labs, a very distributed set of hospitals, different research institutions – you have to look at your fragmented market, do that sub-segmentation analysis and understand how to best serve, in the most productive way, your customer base.

And making sure our San Diego leadership is attuned to the fact that while you may have bigger labs and service providers in the US, over time, having a very distributed set of innovators in France, Germany, could actually drive more success. Because ultimately, you want as much science and as much genomics in as many places as possible to facilitate not only the success of the company but also of the industry. So it's not just about the technology, it's about the people it's about the skills, the buy-in from governments. An example is our partnership with Genomics England and there are many other

country-based genomic medicine programs in the works all wanting to take advantage of precision medicine and having a more integrated approach to healthcare.

You mentioned the importance of sub-segmentation and understanding better what it is customers want. What sort of feedback have you received? What is it that customers are looking for in terms of genomic innovation?

It's not just one answer, of course. It's a pretty broad mix. Despite the massive price impact that we've seen [in the market for genomic analysis technologies] in the last 10 years, people continue to want lower prices. They are also more and more concerned about an end-to-end solution and really thinking in terms of from-sample-to-answer. Ultimately, they don't just want to look at the specs of our machine, they want to look at the end-result. So, it is important for us to be mindful – especially in the clinical space – how they get that end report so they can advise their patient.

How do you see Illumina's EMEA commercial operations and/or the European genomics landscape evolving five years from now?

I think our mix between clinical and research will change. Clinical will become more predominant. I do think you will see new industries crop up in Europe that haven't yet emerged. For example, the consumer genomics market place in US has been tremendously successful with customers like ancestry.com and 23andme. Today, in Europe that is still a very small business and I think that is an opportunity for the consumer genomics market to pick up.

You'll also likely see more collaborations between Illumina, pharma companies and other large players to focus around precision medicine. There will also be more integrated population-based health care, where genomics will be a core component of a country's health care system and Europe will lead in that, with the uniqueness of our market here. That's how I see our next five years will be.

Of course, we will continue to very much focus on our research institutions: we are now segmenting that part of the business – we have research, we have clinical research, peer clinical and other domains and everything is becoming closer together. It's an exciting time.

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Apollo Endosurgery Inflates Coffers With $36m

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Apollo Endosurgery Inc. has raised $36m in a public offering of 6,542,453 shares of common stock, which included the sale of an over-allotment of 853,363 additional shares. The anti-obesity device company had sold the shares at its set price of $5.50 per share. The offering closed on July 25, with Craig-Hallum Capital Group LLC and Roth Capital Partners acting as joint book-running managers.

The Austin, Texas-based company has seen slow sales in the last couple of years and will use proceeds from the offering to support adoption of its endo-bariatric products and development of new product lines and expansion into new markets. *(Also see "Apollo Endosurgery Seeks To Raise $31m In Share Sale" - Medtech Insight, 25 Jul, 2017.)* The company's portfolio of products consists of surgical and non-surgical interventional devices for the treatment of obesity. It inherited the *Lap-Band* gastric band and *Orbera* intragastric balloon technologies through its $110m acquisition of **Allergan PLC's** obesity intervention division in 2013.

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Atlantic Appoints New Chairman

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Irish device firm **Atlantic Therapeutics** has named Gordie Nye as its new chairman. The Galway-based company commercializes *Innova*, an externally applied therapeutic device that delivers electrical stimulation to treat stress urinary incontinence. *(Also see "Start-Up Spotlight: Atlantic Therapeutics, Stimulating The Stress Incontinence Market With Vaginal Mesh Alternative" - Medtech Insight, 5 May, 2017.)*

Nye is currently CEO of R2 Dermatology, a start-up commercializing an aesthetic dermatology technology from Harvard University. He served as CEO of Zeltiq Aesthetics, maker of the *CoolSculpting* "body-contouring" system from 2009-2012. The company was acquired by Allergan for $2.5bn in Feb. 2017. *(Also see "Allergan Pays $2bn-Plus For Zeltiq, Expanding Aesthetics Business" - Medtech Insight, 13 Feb, 2017.)*. He has also held leadership roles in other privately-held companies including **A-Company Orthodontics** and **Critikon**. Atlantic Therapeutics CEO Steve Atkinson previously teamed up with Nye at Zeltiq and Critikon.

Prior to moving into the medical technology industry, Nye held a variety of marketing, sales and general management roles for companies including Gillette and Reebok. His experience in consumer marketing will be used to drive consumer adoption of Innovo.

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Abbott's Devare On Keeping Pace With Viruses And Effective Testing

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Viral hepatitis is now recognized as a major public health challenge, with over 300 million people worldwide estimated to be carriers of hepatitis B or C virus infections in 2015. However, only a small proportion of this population had been tested and were aware of their status, according to data from the World Health Organization's Global Hepatitis Report 2017

As part of efforts to address this challenge, pharma and IVD firm **Abbott Laboratories Inc.** is considering ways to include India – which has a high prevalence of viral hepatitis – in its Global Surveillance Program. The program currently has a library of over 60,000 patient samples with different strains of HIV and hepatitis B and C from six continents and 40 nations. Sushil Devare, Director, Diagnostics Research and Distinguished Research Fellow at Abbott, was in India as a panelist at an event organized by the WHO, the Indian government and the Institute of Liver and Biliary Sciences to mark World Hepatitis Day on July 28. He tells *Medtech Insight* how the company's surveillance program is helping the company "stay ahead" of HIV and hepatitis viruses, enabling it to develop assays that reliably detect and monitor infections.

Sushil Devare, Director, Diagnostics Research, Abbott

Medtech Insight: Abbott launched its first hepatitis test in 1972 and its non-radioactive hepatitis screening test in 1974. Could you take us through some of the key highlights on how the science of diagnostics in the hepatitis C area has evolved alongside mutation of virus strains?

Sushil Devare: Abbott has been at the forefront of innovating diagnostic tests for viruses over the past many decades. With over 40 years of diagnostics leadership as the inventors of the first [US] FDA-approved HIV test and the first FDA-approved Hepatitis C (HCV) molecular genotyping test, Abbott has brought a number of other breakthrough innovations in the space.

Specific to HCV, in 1990, Abbott launched the first HCV EIA (Enzyme Immunoassay), which used only one non-structural HCV protein; in 1992, Abbott developed the second-generation HCV EIA. Platforms for diagnostic analysis have also evolved over the past three decades. In the last decade, we launched HCV tests based on magnetic-particle immunoassays, which utilize chemi-luminescence detection. The evolution of assays has improved sensitivity and specificity of the assays over the years.

Over the past few years, Abbott has also launched the HCV Core Antigen test, which enables diagnosis of HCV in people with active viral infection. Because diagnosing and treating HCV can require more than one diagnostic test, this test can confirm active infection, which helps enrollment into anti-viral treatment, and can lead to a cure. Prior to the availability of this test, the only way to detect active viral infection was using nucleic-acid testing (NAT). Today, as an option, the same infection could be detected using HCV core antigen tests.

Specific to the evolution of diagnostic science alongside mutation of virus strains, the development of tests and platforms over the years has accounted for diversity of HCV virus strains.

Some studies have referred to how mutations in Hepatitis C have kept an effective vaccine at bay. What makes the mutations in HCV so complex, vis-à-vis hepatitis A, B that have vaccines?

In terms of genetic variation, one could compare HCV to HIV. HCV has six genotypes and over 30 sub-genotypes and the maximum variation is in the envelope region, which makes it very complex to develop a vaccine that will cover all genotypes effectively.

In addition, for HCV, there are anti-viral treatments available, which could cure an individual after 12-24 weeks of therapy.

Some 11 countries including China, Brazil, India and Indonesia account for almost 50% of the global burden of chronic hepatitis and just 20% of HCV-infected people had been tested and diagnosed as per WHO data. Would you say WHO's goal of eliminating hepatitis as a public health threat by 2030 is a bit ambitious currently?

The majority of people infected globally with HCV are not aware of the infection because they are asymptomatic. What is not diagnosed cannot be treated.

At the same time, an infected person has the virus replicating at the rate of a trillion viral particles per day. By the time clinical manifestation occurs (such as acute liver failure, cirrhosis and liver cancer) options for addressing these conditions may become limited.

So diagnosis becomes the key step in enrolling for treatment, leading to cure and eliminating HCV. With proper diagnosis, and rendering of treatment, the goal of eliminating hepatitis by 2030 may be achievable.

The WHO reports that nucleic acid tests that are required to make treatment decisions are more expensive ($25–200), and need to be made available at lower cost. Is Abbott working on developing some such affordable options or other new tests/ point of care tests for HCV infection?

The HCV Core Antigen test addresses the issue and is an affordable option. Abbott has applied for regulatory approval for introducing the HCV Core Antigen test in India.

The WHO and the European Association for Study of Liver Diseases (EASL) recommend the use of HCV Core antigen instead of nucleic acid tests (NAT) in situations where NAT is not accessible or available.

Could you share some specifics on Abbott's long-running Global Surveillance Program in the hepatitis C area; any worrying trends in the Asian region that perhaps needs sustained focus?

Hepatitis (and HIV) can evolve to produce different strains and Abbott is committed to ongoing research to ensure that our diagnostic tools keep pace with these viruses. We developed the first HIV test in 1985 to help make the world's blood supply safe again and remain committed to research that allows us to remain vigilant with HIV and other evolving viruses, such as hepatitis B and hepatitis C.

Abbott's Global Surveillance Program is foundational as we seek to stay ahead of HIV and hepatitis viruses. We scour the world for variations of the virus. We keep those samples in our 'vault' so we can diligently compare and identify new variations. This is important because our tests are used around the world and we need to be able to detect the different viral strains.

Abbott's Global Surveillance Program has a library (aka 'vault') of more than 60,000 patient samples that contain different strains of HIV and hepatitis B and hepatitis C from six continents and 40 countries such as the US, Brazil, Argentina, England, Spain, Senegal, South Africa, Saudi Arabia, Israel, Russia, Australia and Thailand. We are also exploring ways in which India is also a part of the program.

Abbott has identified and characterized 5,000 HIV strains, enabling diagnostic tests to detect a wide range of the virus. We have identified and characterized rare HIV Group N and P viruses and are one of only two institutions in the world to have done so, for the P virus strain.

This program has helped improve diagnostic techniques, especially since assays have to be constantly monitored to take into account mutations in viruses and other external factors.

Specific to the Asian region, we have collected several thousand samples that help us to identify genetic variation in the region. Genotype 3 is the pre-dominant strain of HCV in the Asian region.

Any new, ongoing R&D project in hepatitis C diagnostics that you believe can probably be the next big thing in the segment? Any potential for CRISPR Cas9 in HCV?

Abbott's viral discovery efforts continues to look for new viruses which may be implicated in hepatitis. Our work, in collaboration with the University of California in San Francisco (UCSF), has resulted in the discovery of human pegivirus-2 (HPgV-2), which is found in people infected with HCV. The role of HPgV2 in the clinical manifestation, if any, is yet to be elucidated.

HCV does not integrate into the human genome, so the utility of CRISPR Cas9 in HCV may be limited. An HCV infection can be cured using anti-viral therapy.

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CONTINUED FROM PAGE 1

(countries outside of Japan, the US and Europe) with sales expected to rise from $199.9m in 2016 to $600m by 2021, a CAGR of 24.6%.

Growth drivers include an expanding aging population with cardiovascular disease and expected new approvals of TAVR systems. But there are also other factors at play in emerging markets that are less prevalent in the developed world. Rising rates of cigarette smoking rank among them.

Whereas rates of cigarette smoking have dropped significantly in the developed world in the last decades, more people continue to light up in developing countries – such as in the Middle East, African countries and China – a key risk factor for developing aortic valve disease. Rheumatic fever is another driver for aortic valve disease in these parts of the world, with many symptomatic aortic stenosis cases remaining untreated.

Meanwhile, in the US, which accounted for 51.6% of all transcatheter heart-valve management product sales in 2016, obesity, a growing aging population, and the high prevalence of diabetes are leading risk factors for rising heart-valve disease. In the US, sales of TAVR systems are expected to rise from $1.5bn in 2016 to $3.1bn by 2021, a 16.1% increase.

In Europe, which ranked second in terms of total transcatheter heart-valve management product sales in 2016 with an estimated 40.3% market share, sales are expected to see the slowest growth globally from $1.2bn in 2016 to $2bn in 2021, a CAGR of 12.3%.

TAVR - OVERVIEW

TAVR has seen significant innovation in recent years. Many health experts believe that this ground-breaking technology will not only continue to expand geographically, but is very likely to expand to lower-risk and younger patients in the not-too-distant future.

Asked whether they agreed with *Meddevicetracker's* assessment that transcatheter repair and replacements systems would surpass invasive surgical replacement procedures by the end of the forecast period in some regions, two US-based interventional cardiologists expressed little doubt.

TABLE 1

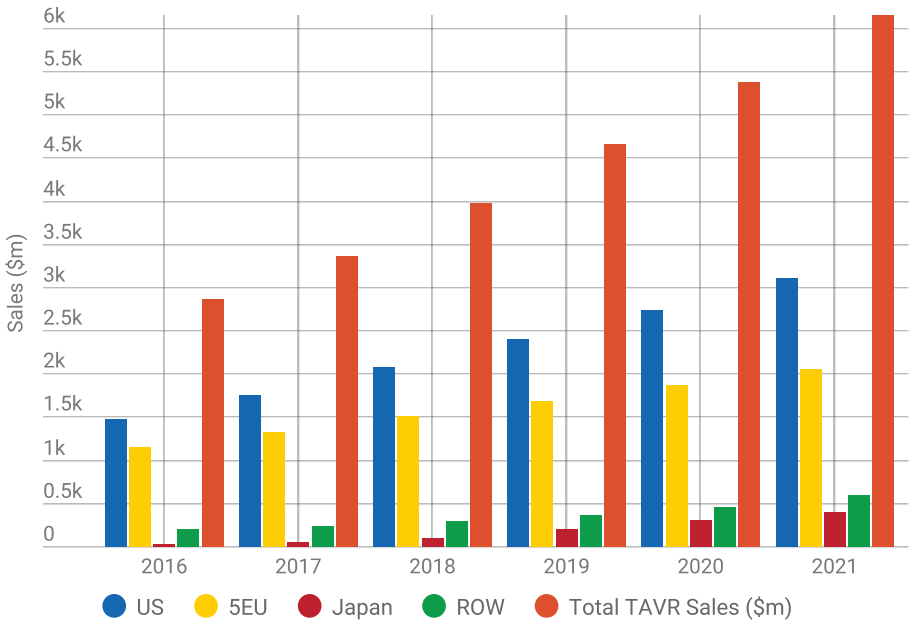
Global Heart-Valve Repair And Replacement Devices Market Share, By Product Type, 2016 and 2021

MARKET SEGMENT	ESTIMATED MARKET SHARE, 2016 (%)	ESTIMATED MARKET SHARE, 2021 (%)
Invasive	41	24
Emerging Transcatheter	59	76
Total Sales ($m)	$4,834.7	$8,094.4

Notes: Estimated sales are for heart-valve repair and replacement devices, which include surgical heart-valve replacement, surgical heart-valve repair, PBV, TAVR, and transcatheter mitral-valve repair. "Heart Valve Repair and Replacement Devices Market"
Source: Meddevicetracker

FIGURE 1

Global Transcatheter Heart Therapy System Sales, By Country/ Region, 2016-2021



Source: Meddevicetracker

Dr. Peter Pelikan, director of the Cardiac Catherization Laboratory at Saint John's Health Center in Santa Monica, California said it is "absolutely" his belief that TAVR will continue to revolutionize the industry.

"If you're asking me what I believe, I believe that almost all aortic-valve replacements will be by TAVR in the next five years," Dr. Pelikan told *Medtech Insight*. "Mitral and triscupid, I don't know that I feel that definite about it. We need more data."

Dr. James Mohyi, chair of cardiology at the Wyandotte Henry Ford Hospital in Detroit, Michigan, was equally optimistic.

"These procedures have revolutionized how we treat patients with advanced heart disease," Dr. Mohyi told *Medtech Insight*, adding that the miniaturizing of instruments has been key.

In 2016, almost 90,000 TAVR procedures were performed globally; of those 50,000 procedures were performed in the US.

Meddevicetracker expects that worldwide TAVR sales will reach $5.5bn by 2021, up 17.1% from $2.5bn in 2016. The three largest competitors in this market are Edwards Lifesciences, Medtronic and St. Jude Medical/Abbott.

That is aside from unforeseeable changes driven by product launches, mergers and acquisitions and expanded market penetration in the emerging markets, with limiters such as the high cost for the valve and a lack of long-term evidence of proof remaining.

Competitive Landscape

Since Edwards Lifesciences became the first company to win the CE mark in September 2007 with its *SAPIEN TAVR* system, the Irvine, California-based company has held the leading position on the global market by making continued improvements and scoring more regulatory victories.

In 2016, Edwards Lifesciences accounted for 65.7% on the global market share with corresponding product sales of $1.6bn followed by Medtronic, which held a 28.2% share with total sales of $698m worldwide, according to *Meddevicetracker*.

Medtronic entered TAVR in 2007 with its transfemorally delivered *CoreValve* system, but didn't receive FDA approval until January 2014, which left Edwards Lifesciences with a major US market advantage for years.

Other competitors in the TAVR segment, including **Boston Scientific Corp.**, St. Jude Medical, **JenaValve Technology GMBH**, **Symetis SA** , **Direct Flow Medical Inc.** (now defunct) and **Braile Biomedica**, accounted for the remaining 6.1% market share and $152.3m in sales with most of the sales being done in Europe.

In 2016, Edwards Lifesciences had $989.5m in US TAVR sales, accounting for a 73.9% market share followed by Medtronic, which had $350m in US TAVR sales and a 26.1% market share.

Edwards Lifesciences is currently selling its third-generation TAVR product, Sapien 3. Recent findings from the PARTNER II trial found that the Sapien 3 valve had shown superiority over surgery in intermediate-risk patients. Based on these results, the FDA expanded the indications for the company's SAPIEN 3 and *SAPIEN XT* transcatheter heart valves for use in in intermediate-risk aortic stenosis patients, making it the first TAVR to obtain this indication in the US *(Also see "US FDA Approves First Intermediate-Risk Indication For TAVR" - Medtech Insight, 18 Aug, 2016.)*. On June 5, Edwards Lifesciences also obtained an FDA panel-track supplement approval for its Sapien system for "valve-to-valve" procedures *(Also see "US Approvals Analysis: FDA Delivers Strong Half-Year Volumes" - Medtech Insight, 19 Jul, 2017.)*.

With Medtronic's announcement on July 10 that it won expanded FDA approval for its *CoreValve Evolut* transcatheter aortic-valve replacement platform *(Also see "US FDA Green-Lights Medtronic's CoreValve Evolut For Intermediate Risk" - Medtech Insight, 11 Jul, 2017.)*, Edwards LifeSciences systems will now face competition in this market segment. Medtronic also recently released positive data from the SURTAVI trial *(Also see "EuroPCR 2017: TAVR Continues To Beat Surgery; Bioabsorbable Stents Not Going Away" - Medtech Insight, 22 May, 2017.)*, which compared 863 intermediate risk patients treated with CoreValve and *Evolut R* systems (FDA approved in 2015) to 794 surgical patients *(Also see "ACC 2017: SURTAVI Supports Intermediate-Risk Intervention For Medtronic's CoreValve" - Medtech Insight, 21 Mar, 2017.)*.

Despite stiffer competition from other TAVR suppliers in Europe, Edwards Lifesciences held the top position with a 55.2% market share and $520m in sales in 2016 in that part of the world, aided by the release of its second- and third-generation SAPIEN products.

Medtronic was the second-leading supplier of TAVR systems in Europe with an estimated 30.8% market share and sales of $290m in 2016.

Other TAVR suppliers in Europe include Boston Scientific, St. Jude and JenaValve. Europe's No. 3 TAVR supplier, Boston Scientific, bought its smaller Swiss rival Symetis for $435m in March *(Also see "Symetis TAVR Buy Not About Throwing Shade On Lotus, BSX Insists" - Medtech Insight, 30 Mar, 2017.)*

Looking East, the approval of Edward Lifesciences SAPIEN XT in 2013 offered a first alternative to Japan's growing aging population with severe aortic stenosis, which favors minimally invasive techniques over surgery.

Medtronic entered the Japanese market in 2016 with the approval of its CoreValve Evolut R system. Both companies are currently the only approved vendors to market their respective TAVR systems in Japan.

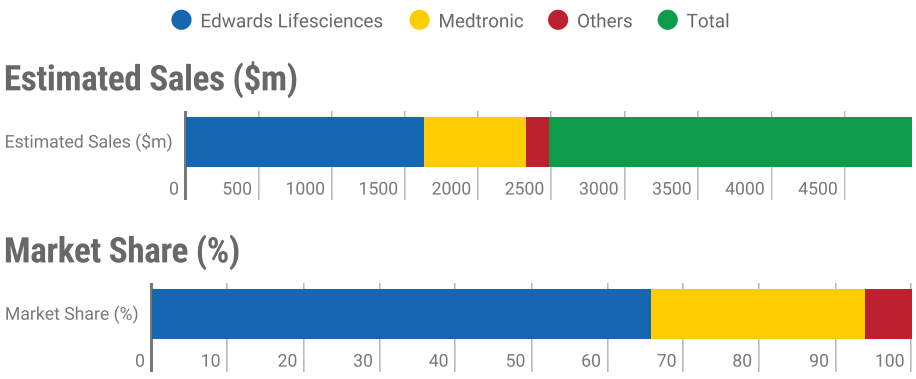
Growth Drivers: Intermediate-Risk, Potential Low-Risk Expansion

When it comes to growth drivers for TAVR, the expanded indication for intermediate-risk patients in the US and Europe is critical, Drs. Pelikan and Mohyi agreed.

Other health experts also believe that on-going studies in low-risk patients could lead to a much broader expansion of TAVR systems. The intermediate group

FIGURE 2

Global TAVR System Market, Share, By Supplier, 2016



Source: Meddevicetracker

is generally defined as those with a surgical mortality risk of 3% at 30 days following the procedure.

Both Edwards Lifesciences (PARTNER 3 with Sapien 3) and Medtronic (CoreValve Evolut R) have on-going studies in low-risk patients with their respective technologies. There are also on-going studies in Europe with low-risk patients such as the UK TAVI registry and NOTION 2, a Scandinavian study.

Meanwhile, Mohyi and Pelikan pointed out that the expanded indication to intermediate-risk patients has already led to a significant increase in TAVR procedures at their respective hospitals.

"At Henry Ford last year, we had 250 TAVR procedures, and then we had 30 surgical replacements of the aortic valve," Mohyi told *Medtech Insight*.

"People are learning about it (it's a new procedure), but the expansion to intermediate-risk patients has really increased the volume significantly," Pelikan added.

Both doctors noted that interventional cardiologists are also using TAVR for off-label uses, adding to the growth in this segment. At Saint John's Hospital, some doctors are using the TAVR valve in the mitral position, Pelikan said. The same is true at Henry Ford Hospital, according to Mohyi.

Then there are the many benefits of using TAVR vs. open surgery.

While Pelikan acknowledged that there is reluctance on the part of some physicians to implant a TAVR valve in somebody who's got a 20- or 30-year life expectancy – "we have no idea what these valves are going to do long-term; we know what they're going to do five years, but not 15 or 20 years," – he maintained that TAVR still beats open heart surgery in every aspect. This includes the benefits of being able to do the procedure with the patient under moderate sedation; patients leave the hospital in two days on average with little discomfort in their groin as opposed to doing open surgery where patients face a five-day hospital stay on average, then leave the hospital with a chest that's held back together with wires and take months to recuperate.

WATCH

See how these transcatheter heart devices work here http://bit.ly/2vlcSA7

"So, it's much quicker and safer and easier on the patient. When I say safer, the complication rate is probably similar, but the discomfort and recuperation rate is so much better than other than these long-term issues, I don't think anybody would favor surgical valve replacement," Pelikan said.

as intermediate risk. The remainder are categorized as too high risk for surgical replacements, making them ideal candidates for TAVR.

"Now that we're moving to less and less sick patients who really could be surgical candidates, we want to look at the research very carefully and make sure it's the right thing for that group," Pelikan noted.

> "If you're asking me what I believe, I believe that almost all aortic-valve replacements will be by TAVR in the next five years," Dr. Peter Pelikan says. "Mitral and triscupid, I don't know that I feel that definite about it. We need more data."

When asked to compare the two rival devices, both doctors said they favor Edwards Lifesciences' Sapien system over Medtronic's CoreValve, citing ease of use, scientific evidence and habit as the main reasons.

"With the Medtronic device, you don't need to rapidly pace the heart, so it's in some ways less stressful to the heart to put in, but I'd say especially with the newest of the Edwards' valves, most people are much more frequently using the Edwards valves," Pelikan said. "The deployment process is just inflating the balloon and you're done."

Mohyi also praised Edwards LifeSciences Sapien XT valve for its ease of use, saying it's less bulky and easier to maneuver.

Hurdles

However, like every device, TAVR systems are not without its problems. Two of the biggest hurdles in the TAVR segment are durability and cost.

Compared to surgical aortic heart-valve replacements, TAVR is a relatively new technique and there is a lack of clinical evidence that these valves will last for decades like their surgical counterparts.

About half of all patients diagnosed with narrowing aortic valves are at low risk for open replacement valve surgery, and 30-40% of patients are categorized

Mohyi said most people he sees who are TAVR candidates are very sick and older who wouldn't survive the surgery. He said for younger patients in their 40s and 50s, he would still use a mechanical value, given its proven durability to last 30 to 40 years.

"The downside is you have to go on blood thinners, but (on the upside) you don't have to go through surgery again," Mohyi said.

Cost is also a significant challenge.

TAVR prices vary, but on average they run around $32,000, which compares to the average sales price of $5,000 to $7,000 for a surgical replacement valve.

Cost comparisons looking at overall cost of TAVR compared with surgical valve replacement found that patients treated with TAVR had reduced hospital stay and intensive care unit stays, but that didn't offset the cost for the TAVR system, according to *Meddevicetracker*.

Pelikan agreed that for most hospitals, TAVR is a money-losing proposition. Up to 20% of patients who underwent TAVR required a permanent pacemaker, adding further costs to the procedure.

This also makes TAVR cost-prohibitive in many parts of the world. Europe has been using the "minimalist approach" of performing TAVR without general anesthesia,

which has led to significant cost savings. That program is now beginning to take hold in the US as well.

TMVREP - OVERVIEW

When it comes to TMVrep, the hope is that the success of TAVR will eventually translate into serving the much larger pool of MR patients.

In 2015, several companies in the industry including Edwards Life Sciences, Medtronic, **HeartWare International Inc.** and Abbott Laboratories Inc. have done strategic acquisitions to address the TMVrep market, which some believe is significantly larger than TAVR *(Also see "Despite Unknowns, Companies Bet On Transcatheter Mitral Valve Repair" - Medtech Insight, 14 Jan, 2016.)*.

According to published reports, there are at least 26 new devices vying to make their way into the TMVrep space, some of which are listed in here *(Also see "Europe's TAVR No. 4 Buys Into Mitral Valve Space" - Medtech Insight, 14 Feb, 2017.)*.

Many health experts, however, believe that the roadblocks to bringing breakthrough TMVrep technologies to market will be steeper than for TAVR.

Challenges include clinical issues such as anatomical and technical problems relating to the mitral valve compared to the aortic valve and other issues such as reimbursement, deliverability, and market segmentation.

> "The TAVR is like a religious experience, and when you see it happen, it almost always helps the patient," Pelikan said. "The MitraClip sometimes helps, but sometimes doesn't."

Currently, the only FDA-approved TMVrep product available in the US is Abbott's *MitraClip*. The edge-to-edge system has been available since 2008, when it received the CE mark. It is the only approved system in the US and Canada for patients with valve disease from degenerative causes, according to *Meddevicetracker*.

The MitraClip however, has had its share of problems.

In March 2016, Abbott issued a voluntary recall of all MitraClip devices distributed in the US between Aug. 28, 2015 and Feb. 3, 2016 due to an issue with the delivery system deployment process. The FDA had warned that the use of the recalled MitraClip products may cause serious injury or death. At the time of the recall, there were 3,534 devices on the market, with nine reports of this malfunction and one death, according to *Meddevicetracker*.

On a more positive note, a recent registry analysis showed that about 91% percent of patients with primary mitral regurgitation therapy had procedural success with the MitraClip, according to a study published online in the *Journal of the American College of Cardiology* on March 7.

In the study, researchers evaluated data from 564 patients who were part of the Society of Thoracic Surgeons (STS)/ American College of Cardiology (ACC) Transcatheter Valve Therapy (TVT) registry.

Pelikan, who has used Abbott's MitraClip, said in his experience the device is sometimes magical, and sometimes it isn't.

"The TAVR is like a religious experience, and when you see it happen, it almost always helps the patient," Pelikan said. "The MitraClip sometimes helps, but sometimes doesn't."

He joins the ranks of others in the industry and health professionals who believe that a valve replacement would be a much better option than a clip, but said more research is needed.

Competitive Landscape

According to *Meddevicetracker*, total worldwide sales of TMVrep systems – which includes sales of edge-to-edge mitral-valve systems, enhanced coaptation/leaflet spacing, coronary sinus annuloplasty devices and chordal systems – will rise from $373.7m in 2016 to about $700m in 2021, a CAGR of 13.4%, driven in large part by the rising aging population and growing prevalence of mitral-valve regurgitation.

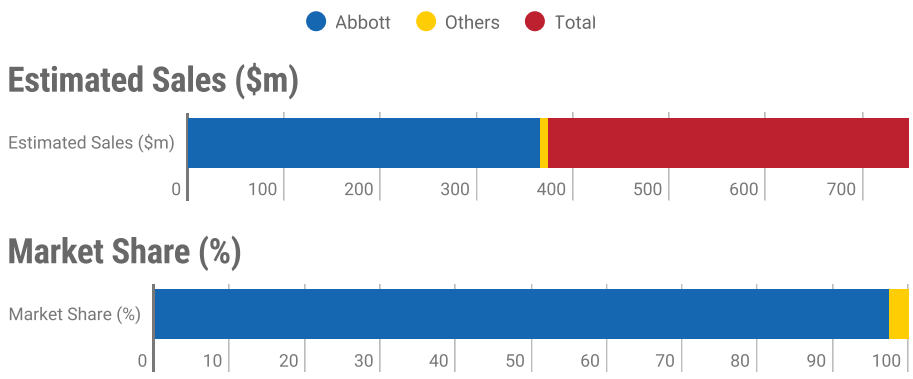
The number of suppliers of TMVrep products in 2016 were limited to a select number of companies.

Abbott dominated the global market of TMVrep systems in 2016 with an estimated market share of 97.4% and corresponding product sales of $364m.

Being first to market with a TMVrep system and having well-established distribution channels have helped Abbott maintain its lead position and *Meddevicetracker* expects that product sales will continue to grow at double-digit rates.

FIGURE 3

Global TMVrep Systems Market, Share, By Supplier, 2016



Source: Meddevicetracker

Positive data from the COAPT trial, designed to test MitraClip in functional mitral regurgitation would greatly expand the cohort of patients, but the trial has reportedly struggled until recently to reach its enrollment target of 610 patients. COAPT results are anticipated in 2018.

Meanwhile, the remaining suppliers of TMVrep devices **Cardiac Dimensions Inc.**, **NeoChord Inc.** and **Valtech Cardio Ltd.** accounted for a 2.6% market share and had $9.6m in sales in 2016. Edwards LifeSciences purchased Valtech this January for $340m *(Also see "Edwards To Pay Up To $690m For Cardioband-Maker Valtech" - Medtech Insight, 28 Nov, 2016.)*.

All three repair devices target different aspects of mitral-valve pathology and are positioned to enter US investigational device exemption trials, according to published reports.

Growth Factors

Among the biggest growth drivers in the TMVrep market is the rising number of patients in developing countries who are ineligible for surgery due to risk factors and the growing body of evidence that supports the use of TMVrep over optimal medical therapy, according to *Meddevicetracker*.

> "I think it's a field in evolution and I don't think I can pick up which way it's going to go, but hopefully they will be better than the MitraClip," Pelikan says.

Cardiac Dimensions' *Carillon* indirect annuloplasty system received the CE mark in December 2009 and has shown in studies to significantly reduce annular dimensions, improved MR, reduced heart failure symptoms and demonstrated greater functional capacity in patients with functional MR *(Also see "Cardiac Dimensions Launches IDE Trial of Carillon Mitral Repair System" - Medtech Insight, 9 Dec, 2016.)*.

The system is currently being evaluated in the landmark REDUCE FMR trial, the first randomized, blinded evaluation of the therapy for functional MR treatment at 25 centers in Europe, Australia and New Zealand.

NeoChord's *DS1000 Artificial Chordae Delivery System* received the CE mark in 2012 and in October 2015 presented two-year follow-up data on 127 patients, which showed sustained outcomes in patients *(Also see "NeoChord Set To Start US Trial Of Artificial Chordae Tendinae System" - Medtech Insight, 2 Jun, 2016.)*.

Valtech, now part of Edwards LifeSciences, developed the annuloplasty *Cardioband*, which received the CE mark in 2015, and according to Meddevicetracker, will benefit from Edwards LifeSciences' experience and distribution channels.

Cardioband is also currently being evaluated in the EU for treating tricuspid regurgitation, with trial enrollment expected to be completed this year.

With more products coming to market, it could lead to pricing pressure that would reduce the high cost of TMVrep, leading to further expansion.

Finally, provided that the COAPT trial warrants positive results, it could lead to a large new cohort of patients for TMVrep, specifically those with functional mitral-valve regurgitation of which few are currently considered good surgical candidates.

To date, therapy is limited to the much smaller cohort of patients in the US with degenerative regurgitation. MitraClip uses the Alfieri approach and is FDA-approved for patients with significant symptomatic DMR at prohibitive risk for mitral-valve surgery.

Meddevicetracker also expects that during the forecast period, a TMVrep product will be approved for use in the Japanese market, which would propel worldwide sales.

Limiters

One of the biggest hurdles in the TMVrep market segment is the lack of scientific evidence. For Pelikan, there remains much to be discovered.

"I think it's a field in evolution and I don't think I can pick up which way it's going to go, but hopefully they will be better than the MitraClip," Pelikan told *Medtech Insight*.

As with TAVR, cost remains a big issue as well as physician training.

Reimbursement is another major hurdle. According to the Centers for Medicare & Medicaid Services data, hospitals spend between $37,000 and $50,000 in acquisition and surgical implantation costs per MitraClip device, and it retails for $30,000, which has led to a significant loss to facilities that use the device, *Meddevicetracker* reported.

In August 2016, the CMS reassigned MitraClip procedures to allow Medicare patients who may benefit from the device broader access. This Medical Severity Diagnosis-Related Group (MS-DRG) reassignment resulted in a 100% increase in base payment rates for the device.

As in most parts of the world, heart-valve disease is still undertreated in the US and there remains ample room for expansion, even as percutaneous procedures rise and continue to supplant surgical procedures.

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