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Court Rules Against Ethicon In Pelvic Mesh Case, But Without Punitive Damages

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A Philadelphia jury awarded $2.16m to a woman who says she was injured by pelvic mesh manufactured by **Johnson & Johnson** unit **Ethicon Endo-Surgery Inc.**, while the corporation moves to appeal an earlier mesh liability case to the US Supreme Court.

The May 26 verdict from the Philadelphia Court of Common Pleas marked the fourth time courts have ruled against Johnson & Johnson on pelvic mesh safety, but was the lowest dollar amount and the first not to include punitive damages. The earlier verdicts against Ethicon were worth $12.5m, $13.5m, and $20m. The $20m verdict was issued on May 5, also in the Philadelphia court *(Also see "J&J Heading Into Fourth Pelvic Mesh Bellwether" - Medtech Insight, 11 May, 2017.)*

The plaintiff, Sharon Beltz, was implanted with the *Ethicon Prolift +M System* to treat pelvic organ prolapse and the *Ethicon Gynecare TVT System* to treat incontinence in September 2006. She has since reportedly experienced chronic pelvic pain and other complications. The jury ruled in her favor after concluding that the risks of the mesh outweighed the cost of making it safer.

But Ethicon saw some victory in the relatively limited award.

"The jury's decision reflects that Prolift performed as expected and was properly designed, and Ethicon appropriately informed the plaintiff's physician of the known risks associated with the product. The jury declined to award punitive damages," said Ethicon spokeswoman Kristen Wallace. "We believe the evidence also showed Ethicon acted appropriately and responsibly in the research, development and marketing of the product, and Prolift was not the cause of the plaintiff's continuing medical problems."

The company is now considering an appeal, she said.

Ethicon has also asked the Supreme Court to review an earlier $3m pelvic mesh verdict, after the 4th Circuit upheld the jury verdict. The company argues that the appellate court was wrong to allow the exclusion of some product review evidence. The case had been the first to go to trial in the multidistrict litigation against Ethicon, which includes tens of thousands of cases.

Separately, fellow mesh manufacturer **CR Bard Inc.** has settled 97 pelvic mesh cases that were part of multidistrict litigation in West Virginia federal court. Judge Joseph Goodwin dismissed the cases as "compromised and settled" on May 26. The dollar amount of the settlements will be available in the company's second quarter financial statement, expected in late July, said company spokeswoman Janine Kramer. In earlier financial statements, Bard said it had set aside $200 million for 3,000 settlements. *(Also see "Bard, J&J Settle Mesh Cases" - Medtech Insight, 28 Apr, 2016.)*

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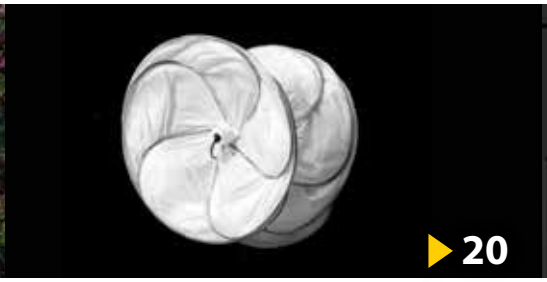
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INS 2017: EU MDR Will Bring Changes, But Devices With Solid Data Will Still Clear Hurdle

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With the EU Medical Device Regulation (MDR) having finally come into force on May 25, developers of high-risk implantable devices now find themselves having to navigate a more complex regulatory landscape. Companies in the growing field of neuromodulation technologies – such as those attending the International Neuromodulation Society (INS) congress taking place in Edinburgh, Scotland, this week – fall in this high-risk device category – as they transition from the Active Implantable Medical Device Directive 90/385/EEC to the MDR, they will undoubtedly encounter changes in the regulatory path towards achieving CE mark for their products.

This will present some challenges, acknowledged Suzanne Halliday, head of medical devices at the notified body BSI Group. In an interview with *Medtech Insight* at the INS Congress' Innovations Day on May 28, she said that one of the key concerns companies will have with the new regulation relates to clinical data.

CLINICAL DATA CONUNDRUMS

"I guess the biggest question is how much clinical data is enough," Halliday noted. "At the moment, we are following MEDDEV 2.7.1 Rev 4 and, in the future, we'll be following the MDR, and the words are that there needs to be sufficient clinical data and the data will have to be scientifically robust and have validity. BSI uses its own technical teams – we have our own in-house clinicians and we also work with external clinicians and statisticians – to help make a decision on whether companies do have enough data." *(Also see "Companies Fear EU Clinical Evaluation Guidance Document Is Becoming De Facto Law" - Medtech Insight, 14 Oct, 2016.)*

While there are fears that the MDR will make Europe a more difficult market to access for device companies, Halliday believes that "if there is good evidence and there is real safety and performance data on the device, then no regulatory body will turn it down – the product will get to market, in any country," she said.

Another big question that BSI often encounters from companies is how they can successfully transition toward compliance with the regulation's new processes and procedures. Here, Halliday emphasizes the need for companies with devices currently on the market to start collecting good post-market clinical follow-up (PMCF) on those products. "Then, when you make a small change to that device, that PMCF data will count towards supporting that small change and getting it approved and into the market, even under the new regulation," Halliday advised. "When there are big changes made to the devices, those are the times when there will have to be a new clinical investigation."

Halliday added that companies must not tarry in gathering that PMCF data. "Do it now because it will really help you. The EU regulation entered into force on May 25 and BSI now gets to apply for designation to be a notified body in six months. It may take us 18 months to two years to get designation because the process described in the MDR is very extensive, so that means the manufacturers have about 18 months to 2 years before they can transition towards the regulation. Good data on their devices, which show the safety and the performance, will help them."

NOTIFIED BODY CHALLENGES

The new regulatory era in Europe will mean a heavier workload for notified bodies like BSI. Coping with the increased volume of devices is one of the organization's key priorities right now.

"The regulation will bring some new devices [into the scope of regulatory bodies], up-classify some devices and change the route of conformity for some devices," said Halliday. "For the first time ever, notified bodies have to issue the product-specific technical documentation certificates for all implants, even if they are class IIb implantable devices," said Halliday. She estimates that BSI could end up with twice as many certificates as it currently does after transitioning all the products that are on quality-management-systems certificates to the MDR's technical-documentation certificates, on top of the forthcoming class IIb devices that its manufacturer clients intend to put out into the European market.

"So the volume is significant for implantable devices. But we are recruiting and training ... and our whole team gets together in June for one week ... to get their initial training in assessing to the new regulations," Halliday told *Medtech Insight*. This training includes practice assessments under the MDR requirements, which will then be used in the notified body's application to be re-designated.

While both manufacturers and notified bodies may very well encounter some bumps along this new regulatory journey, Halliday believes that more collaboration between different stakeholders will help smooth the ride.

"I came to [the INS congress] because ... even though notified bodies have medical doctors in house, we often need real experts in particular areas. At conferences like these, we meet medical doctors who aren't working for the manufacturers directly so they can be considered impartial and they can help us make good, safe decisions. We want to make safe decisions and we want to go as quickly as we can. That's a good way of bringing it all together."

Look for more INS 2017 coverage starting on p. 17.

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Singapore To Make Major Medtech Regulatory Changes Under Economic Growth Plan

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Significant medtech regulatory reforms are the works in Singapore based on work of the country's Committee on the Future Economy (CFE). A report issued by the CFE in February included recommendations impacting all sectors of the national economy, including multiple medtech regulatory reforms.

Medtech industry stakeholders convened May 18-19 at the Health Products Regulatory Forum in Singapore to talk about the device industry's contributions to the country's economy and to debate the key recommendations of the national initiative.

The CFE was conceived in January 2016 to review Singapore's economic strategies and build on the work of its 2010 Economic Strategies Committee. The country has experienced huge, unexpected events over the past decade, in the midst of longer-term structural changes for the global economy and society as a whole.

Global economic growth is subdued, and is expected to remain low, while technological change has been rapid. In addition, global value chains and production patterns are changing, and political uncertainty is a top agenda item almost everywhere.

To forearm and protect Singapore against future developments, 9,000 stakeholders from all parts of the Singapore economy were convened to develop the CFE and the February report. The efforts are targeted at growing Singapore's economy 2-3% per annum for the next decade.

REGULATORY CHANGES AHEAD

Chapter 62 of the final report addresses regulatory needs. It acknowledges that regulations have become less flexible over time, and says the government needs to be nimbler, given the rapid pace of innovation and increasing global competition. "We must take risks and be willing to make fundamental changes to support the emergence of potentially-disruptive business activities," the report's authors say.

Against this backdrop, in the field of medtech regulation, May Ng of the consultancy, ARQon (Singapore), reports that the HSA will be putting in place a range of changes, many of which are significant and all of which are forward-looking.

Subject to Singapore's Medical Device Regulations being updated accordingly, the report proposes to lighten the regulatory burden on economic operators by introducing elements of self-regulation and putting even more emphasis on the post-market phase of regulation. The proposals include:

Pre-Market Consultation Schemes

Two schemes are proposed: one on medical device development (for developers and researchers), and another on pre-submissions (for local registration submission stakeholders) for Singapore registrations. In the first scheme, companies would be supported through developmental phase consultations to promote better understanding of processes by device developers and researchers. The scope would extend to design, technology, intended purpose, validation data, clinical trials, and risk management. The second scheme would cover completeness of the dossier and appropriateness of the supporting documents.

A Singapore Priority-Review Scheme

A priority review option would be established to provide a full evaluation registration route for products that are designed to address unmet clinical needs in five areas of health care: cancer, diabetes, ophthalmic, cardiovascular and infectious diseases. Unmet clinical need would be defined as either a device for which there is no existing alternative treatment or meaningful diagnosis, or a device that represents a breakthrough technology providing a clinically meaningful advantage over existing legally marketed products. The goal would be to reduce turnaround time by 25% by the end of 2018, and by 33% by the end of 2019.

Extension Of Least Burdensome Routes

Further pursuit of the least burdensome approach for manufacturers of Class A (low risk) and Class B (low-medium risk)

devices, improving speed-to-market and reducing compliance costs by making regulatory requirements commensurate with the risk, will be achieved via the following proposals:

- *Removal of the need for Class A sterile products to undergo registration.* This is similar to the methods that are already used for Class A non-sterile devices. This means immediate market access for all Class A devices and no pre-market review. This encourages a self-regulatory approach on the part of manufacturers and dealers, whereby they are required to establish and maintain their quality systems with no third-party certification or QS review needed during licensing;
- *Setting up an online database for the listing of Class A products*. Listing will be mandatory, with penalties applied for non-compliance. Random quality compliance checks will also be made by the HSA. In general, the extension of the self regulation concept places the onus on the company/dealer and puts more focus on post-market controls (as opposed to pre-market reviews);
- *Simplifications for Class A medical device manufacturers, traders and distributors*. These will no longer require: certification under Good Distribution Practices For Medical Devices – GDPMDS (for importers and wholesalers); or ISO 13485 (for manufacturers). Companies will be encouraged to adopt a self-regulatory approach regarding the main quality system that will nevertheless be subject to random quality compliance checks by the HSA;
- *Immediate registration for more Class B devices*. More companies will be able to benefit from immediate registration after a restructure that will see three (Immediate, Abridged and Full routes) instead of five regulatory options for Class B devices. 75% of Class B devices are expected to use the Immediate route. Companies can use this route if the device already has approval from two third countries' reference agencies, or from one country where three years of safe marketing history can be demonstrated. Previously, this Immediate route was available only for devices which had two reference agency approvals both with three years' safe marketing history. Given these positive moves, the two Class B device Expedited Registration (I and II) routes will be discontinued and merged with the Immediate route.

Ng notes that, while no implementation dates were mentioned public at the May 18-19 meeting, she understands that September 2017 is being discussed for the above provisions and changes to take effect.

TELEHEALTH DEVICES

Meanwhile, the ARQon consultant gleans from the HSA that early 2018 is being mooted as the target date for Class B and C standalone mobile apps to begin benefiting from the Immediate medical device registration route, subject to them having already been approved by one reference agency from a list of five other jurisdictions (Australia's TGA, the EU's EMA, Health Canada, Japan's PMDA or the US FDA). These proposals were developed from 150 responses received from a 40-day consultation in late 2016. *(Also see "Singapore Regulators To Streamline Framework For Software And Apps" - Medtech Insight, 21 Nov, 2016.)*

These major regulatory change proposals in Singapore may seem ground-breaking and ambitious, but they will help to set the tone for lighter-touch, swifter regulation for medical devices elsewhere. No information is yet available on fee scales or how the new services will be funded, although the fees for the consultations and priory reviews are targeted by HAS to be "reasonable."

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Asia Reg Roundup: Vietnam On Track Launching New System, Plus Updates From Bangladesh, Hong Kong

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"Industry may or may not be ready, but there is a deadline and companies need to respect it," says Jack Wong of the new rules in Vietnam.

The Asian medical device regulatory space is rapidly developing. "We're always very busy," says Jack Wong, Asia Regulatory Professional Association (ARPA) secretary, and the head of APAC regulatory affairs for a global top 20 medical device company.

And while most of the regional regulatory news is generated in the larger markets and from medtech harmonization efforts by the Association of Southeast Asian Nations (ASEAN), every now and then the smaller markets spring a surprise.

BANGLADESH TEMPORARY HALT ON NEW REGISTRATIONS

Bangladesh did just that on April 1, when the national device authorities ordered a six-month stay on the registration of medical devices – back-dated to January 2017. Registration documents will be accepted by the authorities on a case-by-case basis. "Bangladesh is not a big market in global terms, but the government's stop on registrations will delay lots of approvals," Wong told *Medtech Insight*.

No official reason has been given by the government, but workload and manpower reasons are likely the culprits. Moreover, it's not the first time this has happened; it appears that when certain workload thresholds are breached, the national regulatory staff simply stop accepting most of the new registrations. The Bangladesh authorities will allow imports to continue, however.

The impact on companies is potentially high, but if applicants are able to demonstrate that their products are critical to hospital care, it's possible their files might still be successfully processed. Overseas companies can check on the feasibility of this approach with their local distributors. But applicants might simply be told to re-file in six months' time.

HONG KONG RAMPS UP REGULATORY ACTIVITY

Meanwhile, Hong Kong has been very active of late in the medtech regulatory arena, building its *in vitro* diagnostics regulatory system further and issuing a proposal for the regulation on cosmetic and aesthetic medical devices.

IVDs in Hong Kong are classified into four risk-based categories, classes A-D (lowest-to-highest risk). Medical devices are similarly classified into a four risk-based system, classes 1-4 (lowest-to-highest risk).

Hong Kong's new plans for IVDs are to regulate products in classes B and C, says May Ng, a consultant with the Singapore company ARQon. Currently, all other medical technology devices (except for class 1 medical devices, and class D/highest-risk IVDs) can be submitted for voluntary registration to the Hong Kong Department of Health's (DoH) Medical Device Control Office. Under the new plan, class B and C IVDs will also be subject to the same system of voluntary registration later this year.

In January 2017, the Hong Kong DoH submitted a proposal to the legislative council for the regulation of cosmetic and aesthetic medical devices. All but the lowest-risk cosmetic medical equipment would be regulated and classified into the four risk categories. The timing when such oversight might be implemented, is not yet known, but it is likely that a transition period would be set.

The cosmetic and beauty trade has provided feedback and voiced its objections. Further follow-up by DoH with the legislative council is expected in the second half of 2017.

VIETNAM ROLLS TOWARDS JULY 1 DEADLINE

The establishment of the Vietnamese medtech regulatory system begins in a few short weeks' time. *(Also see "Asia Reg Roundup: Malaysia, Vietnam & India Speed Ahead In 2017" - Medtech Insight, 3 Mar, 2017.)* By July 1, 2017, all class A, lowest-risk medical device applications need to be filed with the regulator. This is the first of several deadlines within the new system, and Wong believes that the date will be adhered to, given that the Vietnam regulator has made a commitment to the country's parliament. Seeking an extension under such circumstances would not be easy. Then again, class A, the most straightforward device classification, is a good place to start, he suggested.

"The system will go ahead, and industry may or may not be ready, but there is a deadline and companies need to respect it," Wong said.

Vietnam is offering the use of third parties for companies to gain classifications for their devices. The third-party service is specifically targeted at companies that don't have experience with classification methods or the Vietnamese system. The government hopes the third-party approach will help outsource some of the most time-intensive Q&A activity with the least experienced product sponsors.

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But it should be noted that these third parties are on a learning curve, themselves, so the process will not be without its hitches. More experienced companies will likely prefer to approach the regulator directly and settle their own classifications, with reference to overseas documentation.

On the issue of manufacturer eligibility in Vietnam, companies need to apply by July 1 for ISO 9001 quality management system accreditation. After that, they will need to pursue most specific ISO 13485 certification.

"Starting with ISO 9000 makes the requirement easer to comply with," said Wong. For this reason, the first deadline should be relatively comfortable. But ISO 13485 compliance is due in 2018. May Ng added, "There will likely be issues when the companies come to apply for ISO 13485 – it's not easy, as companies need to put in place the procedure and train the staff to comply with QMS."

From July 1, importing companies need to provide shipping documentation to the Vietnam Customs Department. For class A devices, that must include an official receipt from the Ministry of Health on dossier quality; and for class B, C and D devices, they must provide an official classification notification and a valid import license.

Despite the transitions, it's so far, so good in Vietnam, in Wong's view. He cautioned that it is still early, and regulatory staff might not fully understand the classification process and documentation needs.

"Companies might say the process is not smooth, but to me, these are typical reactions and totally normal – I feel good about the whole situation," said Wong, who is currently writing a chapter on Vietnamese regulation in his *Handbook of Medical Device Regulation in Asia*. He is also helping to roll out a university-level formal training course in medical device regulation in Vietnam.

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Malaysia Outlines Requirements For Issuing Export Permits

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The Malaysian Medical Device Authority has issued final guidance on the procedure that companies should follow and the documents they should submit when applying for export permits or free sale certificates for their medical devices and IVDs.

The guideline explains that export permits will only be issued for products that are registered under the provisions of the Medical Device Act 2012 (Act 737) and to establishments that hold a valid license under the law. Hence, a company wishing to apply for an export permit should "first obtain an establishment license and register its medical device," the guideline says.

In addition, the establishment applying for an export permit should be a manufacturer or an authorized representative as defined in Act 737 or an authorized agent. Export permits issued by the MDA are valid for two years.

The guideline clarifies that companies would have to submit separate export permit applications for medical devices with different product registration certificates. It states that one application can be submitted for: a registered group of medical devices under one medical device registration certificate; or for a few selected medical devices within a grouping under one registration certificate. "Each application can be for more than one country for export, but individual export permit[s] shall be issued for each requested country," it says.

The guideline lists the various documents and information that companies must submit along with their applications. Any additional information or document sought by the MDA should be submitted within 30 days of the request being made. There is also guidance on the fee applicable for such procedures.

On receiving complete documents and related fees, the MDA says it would aim to issue the export permit approximately within 20 working days.

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UK's Brexit Poses Risks For Device/Drug Combinations

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Some manufacturers of class III device/drug combination products could be in for an expensive and frustrating time once the UK leaves the EU.

Overall, this type of integral device/drug combination, where the drug action is ancillary, is regulated as a device. This means that the device itself needs to be audited by a notified body.

But the notified body must then seek a scientific opinion from one of the competent authorities responsible for overseeing medicinal product regulation -- or the European Medicines Agency (EMA) in certain cases* -- on the quality, safety and usefulness of the drug substance in the combination, as well as the clinical benefit/risk profile of incorporating the substance into the device.

There is a 210-day period allowed for this consultation process, which can be lengthened if there are questions and a need to stop the clock.

These processes have been standard practice under the medical device directives, and will remain in place under the Medical Devices Regulation, which is now being implemented to take full effect in 2020.

The system appears to work relatively well, although there are not many regulatory authorities known for particular expertise in assessing the drug component of device/drug combinations.

The drug arm of the UK's competent authority, the Medicines and Healthcare products Regulatory Agency (MHRA), is one of just a handful of competent authorities with a reputation for being particularly active in reviewing the medicinal product elements of submissions made to medical device notified bodies.

The other authorities with a strong reputation in this area are in Sweden, the Netherlands, and Ireland.

But with Brexit, problems could arise for companies that have relied on the UK's MHRA to review the medicinal product component of a submission. This point was highlighted by Bassil Akra, vice president of the TÜV SÜD notified body for the global focus teams of cardiovascular, orthopedic and clinical, during a May 23 interview with *Medtech Insight* for a webinar recorded in advance of the Knect 365 Medtech Summit, which runs from June 19-23 in Amsterdam.

Companies is this position will need to anticipate potential repercussions on the validity of their certificates. And if it looks as if their certificates will be under risk as a result of Brexit, firms will need to factor in the lengthy period of time it takes to obtain new certificates for the medicinal product element under the new Medical Devices Regulation.

Moreover, if a company must seek the fresh opinion from a designated competent authority in a country that remains within the EU, that presents the risk of a bottleneck. This is because of the lack of remaining expertise in the EU and the fact that there will be one fewer authority designated in drug substances used in device/drug combinations. Also, according to Akra, it is worth keeping in mind that the timelines that the most knowledgeable authorities keep to are already often unpredictable and not in line with the suggested timelines in the legacy directives.

The situation has the potential to raise pressure on the other competent authorities that have specialized in this area. It raises questions on whether the authorities will have enough resources between them, whether they will need to increase their capacity, or will manufacturers will find that timeframes lengthen as they join queues for this process, which has a 210-day deadline anyway.

On top of this, many companies in this field have been inclined to choose a UK notified body because of the close links with the MHRA. But with the future position of UK notified bodies equally uncertain *(Also see "Brexit And The Regulatory Question: Where Are We Now?" - Medtech Insight, 10 Mar, 2017.)*, there will be companies with device/drug combinations that might be in precarious positions.

There are additional potential complications for drugs manufactured by UK pharmaceutical companies, as marketing authorization holders have to be established in the EU or European Economic Area.

In a notice published on the EMA website, the agency reminds industry that pre-

When Is EMA Involved?

The EMA is involved in assessing combinations of medical devices with ancillary medicinal products that are derived from human blood, for example surgical sealants containing albumin, as well as in certain high risk medicines, where the "centralized procedure" is necessary. These include products manufactured using biotechnological processes, for orphan medicinal products and for human products containing a new active substance that was not authorized in the Community before May 20, 2004 (date of entry into force of Regulation (EC) No 726/2004) and which are intended for the treatment of AIDS, cancer, neurodegenerative disorder or diabetes.

Consultation Process For Class III Drug/Device Combinations

1. Scientific advice/pre-meeting
2. Manufacturer submits design dossier, and dossier for competent authority/ European Medicines Agency (EMA) review, to notified body (NB)
3. NB reviews design dossier
4. NB submits "drug" dossier to competent authority/EMA
   •Assessment of usefulness
5. Competent authority/EMA reviews dossier (210-day deadline)
   •Possible request for further information (clock stop)
6. Competent authority/EMA provides a scientific opinion report to NB

The UK submitted notification of its intention to withdraw from the EU on March 29, 2017, which means that – unless there are any further changes - all EU primary and secondary law will cease to apply from March 30 2019. The UK will then become a third country as far as the EU is concerned, the EMA notes.

paring for the UK's withdrawal is not just a matter for European and national administrations, but also for private parties.

This seems to suggest that manufacturers of device/drug combinations will have to assess the position of some of the drug companies, and review where they are established and take action if they are based in the UK.

Remember that for the CE marking of a device incorporating a medicinal product, designated European competent authorities request a European approval of the medicinal product; they do not accept a reference to a file that is reviewed and approved by the US FDA, for example. If the manufacturer has full access to both closed and open parts of the medicinal product file, then the process allows the approval of device incorporating a novel substance in Europe. But, in such a case, the designated authority will do a full review of the drug master file (DMF).

Also, some activities must be performed in the EU (or the EEA), for example, those related to pharmacovigilance and batch release.

The medicinal product marketing authorization holders themselves may be required to adapt processes and to consider changes to the terms of the marketing authorization to ensure continuous validity and use of their products, once the UK has left the EU, EMA says.

If they do not act with enough advance time, there may be a significant impact not only on the continuous supply of medicines, but also device/drug combination products including combined advanced therapy products, within the EU.

EMA has started discussions with national competent authorities on how work related to the evaluation and monitoring of medicines will be shared between member states in light of the UK's withdrawal from the EU. It does not explicitly mention medical devices, but there is no doubt there will be an impact.

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UK's NICE Launching Online Tool To Help Medtech Demonstrate Value

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UK health technology assessment body NICE is launching an online tool to help developers of medical devices and diagnostics understand and generate the evidence needed to show their products are clinically and cost effective.

The Medtech Early Technical Assessment (META) tool, which is scheduled for launch on July 3, is a paid-for service that, according to NICE, is designed to help medtech companies get their products to patients faster. It will help companies identify what evidence they have and what gaps need to be filled to satisfy payer requirements, NICE said.

The tool is expected to help companies prepare for a dialogue with health technology assessment organizations and payers, and potentially speed up time to market. It is aimed at, but not limited to, small and medium sized companies.

"We've designed META to ensure it's both affordable and flexible," said Leeza Osipenko, head of NICE Scientific Advice. "However, we hope that larger enterprises also find the META tool of interest and value for their medtech pipelines," she added.

Partner organizations that work with medtech companies will also be able to license the tool. "These could include academic health science networks, health-care technology consortiums and consultancies who may have their own bespoke approaches to using META and helping product developers prepare their products for adoption into a health-care setting," NICE said. "This accessibility will allow NICE to maximize META's potential and make it available to companies not just in the UK but and internationally as well."

NICE told *Medtech Insight* that it would not be putting any further information about the META tool into the public domain until its formal launch next month in London.

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Maisel Reassumes Acting FDA Device-Evaluation Chief Role As John Sheets Departs

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John Sheets resigned as director of US FDA's Office of Device Evaluation after only 10 months in the position. Device-center Chief Scientist William Maisel has been serving as acting ODE director since April.

"Dr. Maisel assumed the role of ODE director (acting) effective April 10, 2017, after Dr. Sheets announced his intention to depart the FDA to pursue other opportunities," confirmed Angela Stark, a spokeswoman for FDA.

Although Sheets relinquished the ODE chief slot in April, he remained an FDA employee through June 2.

Sheets, who previously worked in the device and biotech industry, joined the agency in June 2016 to head up ODE, which reviews all categories of devices for the US market except *in vitro* diagnostics, imaging and radiation therapy devices. *(Also see "FDA Taps New Office of Device Evaluation Director From Industry" - Medtech Insight, 21 Jun, 2016.)* FDA would not provide a more specific reason for Sheets' departure.

Meanwhile, this is the second time that Maisel has added on the extra duty of running ODE to his portfolio. (Maisel's full permanent titles is CDRH deputy center director for science and chief scientists.) He first became acting director of the office in 2014 after Christy Foreman left the post for FDA's tobacco center. *(Also see "'Acting' At CDRH: Two Top Offices Are Now Run By Interim Directors" - Medtech Insight, 19 Jan, 2015.)* Maisel relinquished the role after Sheets took over in 2016.

The transition at ODE comes as multiple device-review reforms are being implemented based on the December-enacted 21st Century Cures Act, including expanding the expedited access pathway (Breakthough Devices) and humanitarian device exemption programs, updating the standards-recognition process and adding reviewer training activities. Nonetheless, ODE is being run by experienced hands in Maisel, and Deputy Directors Randall Brockman (Clinical), Joynette Foy (Engineering & Science Review) and Barbara Zimmerman (Premarket Program Management).

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Class I Device-Makers Get Wiggle Room As US FDA Pushes UDI Compliance Date To 2020

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Makers of low-risk class I devices have an extra two years of wiggle room to comply with US FDA's Unique Device Identification program thanks to a deadline extension from the agency.

Class I device and unclassified product manufacturers originally had until September 2018 to add UDI to labels, but according to a June 2 letter from FDA to industry, those firms now have until September 2020 to comply. (For class I products that must be directly marked with UDI, the deadline has been pushed to September 2022.)

The two-year deadline shift means firms can sell class I non-UDI-marked product supply through 2023 (or 2025 for direct-marked devices).

> "We plan to engage with industry and other stakeholders to address existing challenges, and optimize the quality and utility of the data for higher-risk medical devices already in the system before adding lower-risk medical devices," CDRH's Thomas Gross writes.

The change in deadline appears to be targeted at giving the agency and industry time to work through challenges posed by incorporating device identifiers into electronic health systems.

"A truly successful UDI system … depends on UDI being integrated into electronic health information throughout our healthcare system, including in the supply chain, registries and electronic health records. To fully reap the public health benefits and a return on investment of a UDI system, high-quality UDI data must be available in standardized ways so that the health-care community can and will use it with confidence," wrote Thomas Gross, director of the Office of Surveillance and Biometrics within FDA's Center for Devices and Radiological Health.

"For these reasons, we plan to engage with industry and other stakeholders to address existing challenges, and optimize the quality and utility of the data for higher-risk medical devices

already in the system before adding lower-risk medical devices," Gross added. "Taking the time to do this now will help ensure the transition from development of the UDI system to widespread use and sustainability."

With some exceptions, manufacturers of high-risk class III devices and class II products, and makers of lifesaving and life-sustaining class II devices already fall under the umbrella of the UDI regulation.

As of May 1, the letter points out, 1.4 million records from more than 4,000 labelers have been entered into FDA's public Global Unique Device Identification Database (GUDID), where all UDI data is stored.

But incorporating UDIs into electronic health systems, including patient records and insurance claims databases, has been a slow-moving process. *(Also see "UDIs Should Be Added To Insurance Claims, Panel Agrees" - Medtech Insight, 2 Feb, 2017.)*

To extend the class I compliance dates, FDA will issue a guidance document "to provide an enforcement discretion policy for labeling, GUDID data submission, standard date formatting, and direct-mark requirements for class I and unclassified devices," Gross wrote.

This isn't the first time the agency has granted UDI deadline extensions. In April, FDA gave manufacturers of soft contact lenses an indefinite reprieve from complying with UDI requirements because of an ongoing technical challenge around adding the lenses to GUDID. *(Also see "Makers Of Soft Contact Lens Get Indefinite UDI Extension" - Medtech Insight, 3 Apr, 2017.)*

And in September 2016, the agency gave a two-year extension – to September 2018 – to makers of convenience kits, repackaged single-use devices, and devices co-packaged or cross-labeled with drugs. *(Also see "UDI Extensions: Convenience Kits, Repackaged Devices, Combo Products" - Medtech Insight, 6 Sep, 2016.)*

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Industry Execs Lobby US Secretaries Ross, Price On Medtech Issues

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AdvaMed CEO Scott Whitaker and a group of device executives met with US Department of Commerce Secretary Wilbur Ross and Health and Human Services Secretary Tom Price May 31. On top of the industry's agenda for the meetings was permanent repeal of the medical device tax and reauthorization of FDA device user fees (MDUFA IV). Reimbursement and trade issues were also discussed.

The primary objective of the May 31 meetings was to open channels of communication directly with the cabinet secretaries, AdvaMed spokesman Greg Crist said. "We have met with senior staff in both departments," he noted. "But this was a good opportunity for our member CEOs to share our industry priorities."

Whitaker joined 11 CEOs or top level-executives of device companies in visiting the Departments of Commerce and Health. Among the medtech executives were Michael Minogue, CEO of Abiomed, and Michael Phalen, president of MedSurg at Boston Scientific.

Secretary Wilbur Ross has jurisdiction over tax and trade policy. Meanwhile, Secretary Price oversees both FDA and CMS.

"The medical technology industry is poised for some seismic advances and growth in the coming years, resulting in lasting change both for patients specifically as well as the health care ecosystem more broadly," said Whitaker. "Our message to Secretaries Price and Ross today was simple: We can be a force multiplier for innovation, job growth and value. And we stand ready to work with this administration and its team to remove barriers and foster a climate for these life-changing technologies."

The two top US policy priorities for industry – repeal of the device tax and reauthorization of FDA user fees – are in the hands of Congress, but cabinet secretaries can be influential.

Industry reached an agreement with FDA to reauthorize user fees, including an increase in fees matched to expanded commitments to performance by the agency, last summer, during the Obama administration. Since then, the Trump White House has submitted a budget that would substantially increase user fees beyond what was agreed to by industry, a request that has not received any traction on Capitol Hill so far. *(Also see "Trump Budget: 71% Of US FDA Device Funding Would Come From User Fees" - Medtech Insight, 23 May, 2017.)*

The industry contingent reiterated to Price its support for the MDUFA IV "agreement as negotiated and would not support reopening the agreements at this late stage," Crist said.

The group also emphasized to Secretary Ross the importance of repealing the device tax, which companies have argued has led to the loss of thousands of jobs and threatens innovation in the sector. Industry was previously successful in achieving a two-year moratorium on the tax, but that is set to expire at the end of this year. AdvaMed, along with other groups, have been pushing multiple possible vehicles for device-tax repeal, including legislation to repeal the Affordable Care Act, as well as other alternatives. *(Also see "Industry Confident About Device Tax Repeal, But It's Still Vehicle-Shopping" - Medtech Insight, 12 Apr, 2017.)*

The executives also discussed trade issues, including what they see as protectionist policies in key markets such as China.

"President Trump made statements during the campaign, and since has made several more regarding trade policy," said Crist. "He has indicated that he is learning and revising his policies. We are keeping our focus on the policies the president actually implements after such consideration and [we] appreciate these meetings to make our case."

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US Officials: Work On Tests To Discern Zika From Dengue Could Slow Without Steady Federal Funding

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US health-care agency officials recently defended their work to control and stop risks from the Zika virus and other mosquito-borne diseases before two House subcommittees. Officials from agencies including FDA, the National Institute of Allergy and Infectious Diseases (NIAID), and the Centers for Disease Control and Prevention argued for a steadier source of funding to support development of anti-mosquito-borne-disease diagnostics.

NIAID Director Anthony Fauci testified at the House Appropriations Labor and HHS Subcommittee hearing on May 17 and the House Energy and Commerce Committee's Oversight and Investigations Subcommittee hearing on May 23. He told the Energy and Commerce Oversight Subpanel that, while current molecular tests for viral RNA can detect Zika during the acute phase of infection and antibody assays can pinpoint prior infections, "Zika viruses may detect and cross-react against other flaviviruses, such as Dengue."

NIAID grantees and investigators "are working to generate antibodies and recombinant protein antigens to distinguish between Zika and Dengue," Fauci said. NIAID is a sub-agency of the National Institutes of Health.

For these reasons, "I think it's a good idea to have a steady funding source," Fauci told Rep. Diana DeGette, D-Colo., at the May 23 hearing, adding, "It was tough to get the dollars we needed, until late last year."

In the summer of 2016, the House and Senate reached a stalemate over emergency appropriations, and adjourned in August without contributing extra dollars for the Zika virus battle. *(Also see "Feds Closer To Dx Distinguishing Zika From Dengue As HHS Tries To Plug Funding Gap" - Medtech Insight, 11 Aug, 2016.)*

The cross-reactivity between Dengue and Zika "makes it difficult to counsel pregnant women about previous exposure to Zika virus," Lyle Petersen, CDC director, division of vector-borne disease, told the Oversight Subcommittee.

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RESEARCH NEEDED ON ZIKA TIME IN BODY FLUIDS

Also, Peterson added, one of the biggest challenges with Zika is that the infection typically causes a mild illness or no symptoms at all, which makes it even more difficult to discern if a woman (whose unborn child could develop microencephaly in the womb if she is infected) or her partner might be carrying the virus. CDC has been trying to research how long Zika can remain in body fluids, such as semen, for example. This, Petersen said, "can inform our laboratory guidance, as well as prevention messaging."

He also commented that Zika and other mosquito-borne diseases are not diminishing over time. "Alarmingly, the emergence of mosquito-borne diseases appears to be accelerating. Because of this, we need to address the threat of vector-borne diseases systematically, rather than episodically, with a steady stream of funds."

Fauci reinforced this, noting, "We need a continuing supply of funds to support our efforts. This is not a sprint, it's a marathon."

FDA ACTIONS

Meanwhile, it's FDA's job to help private diagnostic firms and agency scientists to advance development of diagnostic tests for Zika. FDA is in the midst of "supporting the validation and use of a World Health Organization reference panel to be developed into an international standard for serological assays," FDA's Acting Chief Scientist Luciana Borio noted at the House Energy and Commerce Subcommittee hearing.

After the start of the Zika virus outbreaks in the Americas, and in the southern-most points of the US, including Puerto Rico, FDA made available emergency use authorization (EUA) templates that laid out data requirements for a Zika virus diagnostic EUA. The agency also created reference materials made available to Zika diagnostic manufacturers that had already established analytical performance for their assays. As a result of this, "FDA has authorized the use of 16 diagnostic tests for Zika virus" under its EUA authority, including 13 nucleic-acid-based tests to diagnose active infections, and three serological tests to assess whether individual who recently may have been exposed to Zika, are actually infected, Borio said.

As of May 9, there were 1,845 pregnant women within the US states and Washington, DC, plus 3,795 pregnant women in US territories, "with laboratory-reported evidence of possible Zika virus infection," Borio testified.

Nonetheless, scientists who study mosquito-borne disease are making some progress on a universal vaccine for *all* mosquito-borne illnesses, NIAID's Fauci told the House Appropriations Committee's Labor/HHS Subpanel at the earlier hearing.

"There is this very ingenious approach – I can't tell you yet whether it will be successful – essentially to develop a vaccine against the proteins in the saliva of a mosquito. So that when the mosquito bites, there will be an inflammatory response around the bite area, that will prevent whatever disease the mosquito is carrying – influenza, chikungunya, other flaviviruses or even malaria – to block it, before it disseminates throughout the human body. That's being started right now, at NIH."

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Investors Lay $5m On Savonix's Vision To Make Cognitive Data 'Cheap, Fast, Easy' To Access

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San Francisco-based Savonix, which has developed an evidence-based cognitive assessment mobile app designed to replace conventional pen and paper testing, has raised a further $5.1m in Series A funding. This brings the total investment received by the company to date to $6.6m.

Savonix CEO Mylea Charvat told *Medtech Insight* she plans to use the latest financing to build out the firm's back-end infrastructure for international Protected Health Information compliance, scale the business to global markets, including Japan and China, and to expand its marketing and products team. Charvat, a trained translational neuroscientist, said she'll also hire five employees, bringing the total workforce to 19.

Charvat, who founded Savonix in October 2015, said the *Savonix Mobile app* is unique in that it is the only tool available to score and report cognitive tests with a virtual technician and capture behavior rather than just accuracy and reaction time with its 3D interactive battery of tests.

"We are truly a cognitive testing company," Charvat told *Medtech Insight*. "There's been some digitization where they replace the pen and paper testing with a digital testing kit, but until Savonix, no one had created a virtual clinician that removes the need for a specialist – a very highly paid and expensive, and very rare, specialist – to do the administration, scoring and reporting."

David Kim, CEO at **DigiTx Partners**, which led the Series A round with participation from **Rethink Impact**, also believes that Savonix is poised to transform how the medical community will use mobile platforms and technology to generate critical insights into the cognitive status of an individual.

"Savonix's comprehensive brain evaluation platform improves cognitive testing and overcomes the financial and time burdens of pen and paper methodologies," Kim stated.

Savonix Mobile tests across multiple cognitive and emotional domains including verbal memory, impulse control, focus, sustained attention, emotion recognition, information processing speed, cognitive flexibility, working memory, executive function and visual spatial memory.

HOW IT WORKS

The app is used for clinical care and in clinical trials, Charvat explained. In clinical testing, a specialist orders the test, which generates an email that is sent to the patient with a test code and instructions on how to take the test. Some patients take the test at the doctor's office on a pad; others may take it at home on their own device.

"It depends on how [the clinicians] are seeing their patients: are they remote patients, are they more traditional health care systems or telehealth," Charvat explained.

The cognitive assessment takes 25-35 minutes to perform compared to traditional pen and paper testing, which can take hours. After the test is completed, the patient can view high-level results and information on their phone while the clinician gets very detailed results and information sent to the "Cloud," accessible via a HIPAA-compliant web-based clinical dashboard, she said.

"The dashboard can be accessed by mobile or desktop by the clinician," she said, adding "That's how a clinician would order tests and monitor patient progress."

The company claims that Savonix Mobile allows clinicians to better understand a patient's cognitive health and is used to build treatment plans based on the indi-

Savonix Mobile App

Source: Savonix

vidual's specific needs. Charvat gave the example of a patient being treated for traumatic brain injury where a clinician may prescribe monthly testing to measure cognition as part of a treatment plan and look at different time points to track the patient's progress.

She said using Savonix's approach dramatically reduces patient time and monetary investments, eliminates the risk of missing or incorrect data and improves overall health of patients. The company, however, has yet to publish studies to show that the tool is superior to using conventional methods.

Launched last November, the Savonix Mobile is currently being used by eight customers including biotech companies **Senescence Life Sciences** and **Alkahest Inc.**, New York University and data analytics and neurodiagnostics firm **CereScan Corp.,** Charvat said.

Denver, Colorado-based CereScan contracts with outside physicians and helps them incorporate and interpret clinical data that can be used in treating patients with mental behavioral health issues and brain injuries.

Sean Strauss, VP of Clinical Services at CereScan, told *Medtech Insight* that the Savonix Mobile app offered a "natural fit" for the medtech company to test cognitive function in patients and offer their contracted physicians quick and easy results.

"The historical tests have all been very rudimentary – pencil-and-paper-type based exams – and with us being more of an IT-driven, technology company, it's very difficult to get timely results off paper and pencil," Strauss said. "I was on the hunt for something more useable, more scalable, more scoreable and standardized that didn't have as much variability across the board."

CereScan's team analyzes the patient data from the Savonix Mobile app, and has a team of clinicians that works with contracted physicians to interpret the data.

"We do a fair bit of translating for them (contracted physicians) … that's why we chose Savonix, it's a very easily translatable, easily understandable data set for our providers or the patients who interpret and digest the data," he said.

Thus far, 100 patients have taken the Savonix test and it has shown excellent accuracy, according to Strauss. The gleaned data has shown to eliminate false positives and false negatives that often show up when patients use paper and pen testing due to testing fatigue. He added that CereScan is now using the Savonix test for all of their patients to see how it matches up with other factors in the patient's clinical history.

Maylea Charvat, CEO and Founder of Savonix


Source: Savonix

Other customers, including Senescene and Alkahest, use the Savonix app as a measure of cognition in clinical trials, Charvat said. She added that Savonix also joined forces with an unnamed Fortune 500 health care company of which details will be announced this summer.

LICENSING MODEL

Asked about the revenue stream, Charvat said that Savonix sells its tests based on a licensing model where customers can order bundled tests.

"You can give all of the tests together or you can say we just want this one or we want these three in combination or these four in combination or these two – and you can put all of these different bundles on your license and then that shows up on your dashboard," she explained. "And you can order different combinations of tests for your patients based on what you're looking at with this patient."

The cost per test in the US ranges from $15-60, she said, depending on how tests are bundled. Currently, the app is being offered in the US and in Asia.

MAKING COGNITIVE DATA CHEAP, FAST, EASY

Over the long-term, Charvat hopes that the Savonix app will be the go-to tool for people who otherwise wouldn't have access to cognitive testing, which, she said, is critical to managing most diseases.

"If we think about the most vital organ in the body – and we think we can call the brain an organ – it's the brain and so the fact is cognition emerges as a top three predictor of outcome in every single disease where it's ever been studied," she said. "If you cannot pay attention, remember, think and plan, you cannot participate in your own treatment, whether it's physical therapy or blood glucose monitoring. And if you cannot participate in your own treatment, and you cannot be managed around your cognitive ability, you will not have a good outcome," she said.

She said her husband's situation taught her that lesson first-hand as the wife of a patient and being a trained clinician.

The idea for starting Savonix came to her after her husband was severely injured in a motorcycle accident and unable to walk. She said he was disabled for months and when she realized how difficult it was for patients to gain access to critical cognitive testing and analysis, she wanted to find a solution.

She started the company with $1.5m in seed funding led by RoundGlass Partners, with additional participation from Kickstart Seed Fund, BMNT Capital, and San Francisco-based angel investors Bandel Carano and Connecticut-based Ed Glassmeyer, among others.

"For me, the long-term vision and the reason I did this was to make cognitive data as cheap, fast and easy to get as … your traditional vital signs where you don't need a specialist to get it," he said.

With her husband walking again, and having recently summited Mount Whitney, she pointed out that without her connections in the health care industry and own expertise, the outcome would have been very different.

"It was about breaking the doors down," she said.

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INS 2017: Saluda's Closed-Loop Spinal Cord Stim Tech Sparks GSK-VC Interest; Solid Preliminary Data

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Saluda Medical Pty. Ltd. has caught the attention of yet another big name in the health care industry, with the closing of a Aus$53m ($40m) Series D financing round led by new investor Action Potential Venture Capital (APVC) – the fund set up in 2013 by pharma giant **GlaxoSmithKline PLC** to invest exclusively in bioelectronic medicines. APVC was joined by Saluda's existing shareholders, including medtech's biggest player Medtronic.

The funds will be used primarily to support the Australian firm's clinical activities as it seeks to get CE mark, Australian and US approvals for its flagship product, the *Evoke* spinal cord stimulation (SCS) system.

Evoke has emerged from Saluda's platform technology, a closed-loop neuromodulation system that incorporates a bio-amplifier which continuously records the response of neurons to stimulation (called electrically evoked compound action potentials or ECAPS). The system uses this response to adjust the therapeutic dose of electrical stimulation and automatically deliver this optimum dose to the patient. Current SCS devices, unlike Evoke, do not have this feedback loop and can only give a fixed dose of stimulation. Any changes to the therapeutic regime have to be manually adjusted.

The 24-month Avalon study is currently assessing Evoke in patients with chronic pain of the trunk and/or limbs at five clinical sites in Australia. Preliminary three- and six-month findings from Avalon were presented by lead investigator Marc Russo, of Hunter Pain Clinic in New South Wales, Australia, at the International Neuromodulation Society meeting on May 29.

Of the 36 patients that were permanently implanted with Evoke, 31 patients were available for the three-month follow-up and their average improvement in overall pain was 79.3%. Of the 32 patients available at the six-month follow-up, the average improvement in overall pain 73.8%.

The proportion of subjects with ≥50% pain relief was 92.6% (3 months) and 85.0% (6 months) for back pain and 91.3% (3 months) and 78.6% (6 months) for leg pain. The proportion of subjects with ≥80% pain relief was 70.4% (3 months) and 65.0% (6 months) for back pain. and 56.5% (3 months) and 50.0% (6 months) for leg pain.

Evoke was also associated with improvements in mean pain BPI scores, in quality of life, function and disability and sleep were observed. Additionally, interim programming visits decreased significantly over time, and the level of pain relief experienced by the patients treated with Evoke, at 3 months, in the Avalon study compared favorably to the pain relief at 3 months seen with other SCS systems in other clinical studies

The lead investigator told delegates at the INS congress that while the preliminary findings of a closed-loop SCS system using ECAPs were promising, there was still "a lot of potential for refinement to come." This included better prediction of outcomes and knowing the likelihood of a stimulation dose being effective for a particular patient, as well as being able to identify a neurophysiological signal for failure so the treatment can be preventative rather than reactive.

EVOKE US STUDY: A TONIC TO STANDARD SCS?

Saluda's series D financing will also go towards its US pivotal study, named after the SCS device itself. EVOKE is a randomized double-blinded trial which will compare Saluda's device against standard tonic SCS with fixed dose and no feedback loop. Discussing the details of the three-year study with INS congress delegates, lead investors of the Evoke trial and president of the INS, Timothy Deer of The Center for Pain Relief in West Virginia noted that tolerance and loss of therapy remains one of the last great hurdles in SCS and account for around 25% of explants of SCS devices. Conventional fixed-input SCS technologies do not adjust for the changing physiological conditions and real-time movement and the "encouraging data" from the Avalon study, which shows the potential of closed-loop SCS systems, is "a great step" in advancing neuromodulation as field, he told delegates.

Deer said that the Evoke study is notable in that it has been designed specifically to minimize the inherent bias in company-sponsored studies. The study used the same device for the control and the closed-loop arm and the clinicians, co-ordinators and research staff are blinded to the therapy. The patients are blinded to the hypothesis so they do not know the benefits of either arm of therapy, and their devices are programmed using the same technique and optimized using ECAPs. In the closed-loop arm, one extra step is taken to turn feedback on every five minutes or less.

Additionally, an independent adjudication committee will review all adverse events and an independent medical monitor will review all patients prior to enrollment.

Evoke will enroll around 134 patients in up to 20 sites across the US.

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INS 2017: Positive Initial Data Put Axonics On Next Big Wave Of Sacral Neuromodulation Growth

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Positive initial results from a multicenter clinical study of the *r-SNM system* for treating overactive bladder (OAB) has further consolidated **Axonics Modulation Technologies Inc.**'s standing as a notable rival – despite its modest stature – to medtech giant **Medtronic PLC** in the sacral neuromodulation (SNM) market.

The RELAX-OAB study was initiated in June last year, after the r-SNM system was CE marked, and it has enrolled 51 overactive bladder patients with symptoms of urinary urgency incontinence and urgency. The implantable device works by delivering mild electrical pulses to stimulate the sacral nerves located in the pelvis which control voiding function.

The results, presented on May 30 at the 13th International Neuromodulation Society congress in Edinburgh, Scotland, showed that at one month, 71% of subjects were initial responders to therapy – this is defined as a 50% or greater reduction in incontinence or urgency frequency symptoms, or a reduction to less than eight voids per day in urgent frequency subjects.

At three months, the study found that 91% of the 33 initial responders continued to respond to therapy. Initial responders also reported clinically meaningful improvements in quality of life, underscored by significant improvements from baseline in the ICIQ-OABqol HRQL score of 31.0 points (+/- 4.4, SE, n=23), and over 90% of this group said they were satisfied with the r-SNM system.

There were no serious adverse device effects or unanticipated adverse device effects reported, although two subjects required surgical intervention.

In an interview with *Medtech Insight*, Raymond Cohen, CEO of Axonics, said the results – having come from the company's first human clinical study – marks an important milestone. "It's validation that the product, first and foremost, works as designed; that it's safe and efficacious. We all knew it was going to work but you have to go through that process and it gives confidence to everyone who has been involved in the project and who has worked with us right from the beginning."

The Miniaturized Rechargeable Ipg Of Axonics' r-SNM System

Source: Axonics Modulation Technologies Inc.

The r-SNM system is a third the size of Medtronic's Interstim and a quarter of the size of standard IPGs.

The Irvine, California firm does not have to wait long before RELAX-OAB is completed, with all subjects expected to reach the three-month study endpoint in June and the complete study results will be presented at the International Continence Society annual meeting in September in Florence, Italy.

Cohen is confident that the final results will affirm the positive preliminary findings. He confirmed that the data will be made available to the US FDA, as part of Axonics' IDE application to run a pivotal clinical trial to get premarket approval for the r-SNM system to treat OAB. He said that 12 clinical sites in the US, Canada and Europe have already been selected to participate in the study, which is slated to start in the second half of this year – pending the green light from the FDA. For its part, Axonics is "ready to go," said Cohen.

SMALL AND RECHARGEABLE: INGREDIENTS FOR MARKET EXPLOSION

SNM is not a new technology. Medtronic was the first to bring to market its InterStim SNS device, which was CE marked in 1994 and US FDA-approved in 1997 for the treatment of OAB and urinary retention in patients who do not respond to behavioral therapy and conventional drug treatment. Reimbursement codes for this therapy are already in place in all the key markets worldwide and to date, it is estimated around 250,000 patients to date have been implanted with an SNM device.

Adoption of SNM for urological conditions, like with many neuromodulation therapies, is expected to see exponential growth over the as physicians' experience with these technologies deepen and technical advancements continue. Cohen told *Medtech Insight* that the initial catalyst that sparked growth in SNM was the advent of the tined lead – "putting fish hooks on the lead" – that stops the wire from migrating. "Once that innovation was brought to bear, you saw the market just took off from there," Cohen said. The market will see the same "explosion" with the introduction of Axonics' r-SNM and the benefits that the devices' features – notably its miniature size and rechargeable battery – will bring to patients, he added.

Because Medtronic's *Interstim II* does not have a rechargeable battery, the implantable pulse generator (IPG) has to be explanted every four years or so. The

r-SNM system has been qualified to last at least 15 years. Axonics' IPG is recharged transcutaneously – once every two weeks, for an hour – using an external "puck" that is worn by patient using a belt or adhered temporarily to the skin. Cohen revealed that the firm is working on extending the battery charge so that the IPG only needs to be recharged once a month, making it more convenient for the patient.

Additionally, the r-SNM system's IPG is a third the size of Medtronic's and one fourth the size of standard IPGs used in neuromodulation systems for other indications. With 85% of the OAB patient population being female and the average age being 57 years old, the size of the IPG, which sits in the patient's buttock area, is an important factor in this clinical application, believes Cohen.

"So we're now producing a miniaturized device, with a very long life, and I believe this is going to account for an explosion in this business," he said.

PRECISION TARGETING

As to when the r-SNM system will be pushed out into the market, the CEO said that the plans are for a worldwide launch in 2019, with the hope that the technology will already have US FDA-approval by that time. While the system is CE-marked and the first clinical trial with its promising data is set to complete this year, Cohen has no intention to rush into commercialization. Indeed, the medtech industry veteran believes that too many start-ups and SMEs hurry their products into market far too early, only to find themselves floundering when they are not getting the buy-in from customers (See 'Tip From The Top' below).

Instead, Axonics is now investing in taking the time to gather the necessary intelligence they need to understand the dynamics and landscape of each market it wants to access. "What we're doing is we're being very precise, we want to understand exactly what are the rules associated with reimbursement in every single market," said Cohen, adding that even though SNM is a covered service through Europe, each individual country has a quirk. "What you need to do in France to get market access is different from what it is in the Netherlands or Germany or the UK. You need to be very precise, you need to have all the facts. You need to meet with the agencies that decide all these things and understand if there is some sort of small clinical evaluation that is necessary beyond the CE mark or not, for example.

"One should also know who is doing the volume, what clinical centers are doing the volume with the key opinion leaders in these countries and you need to create those relationships with the KOLs," the CEO advised. "You need to do all those things first before you rush out and say 'I'm going to sign a deal or I'm going to hire direct sales people.' That requires experience, time, judgement so when you launch in a country you are not going out blind. You would have already met those KOLs and sat down with them and found out about their practice and introduced your product to them. So when it's time to launch, you're ready to go. People respect that - a little warm up is not a bad thing."

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Tip From The Top: Timing And Targeting

Raymond Cohen, CEO of Axonics Modulation Technologies, believes in patience pays off when it comes to taking your product to market. In a Q&A session at the INS 2017 meeting in Edinburgh, Scotland, he said that the single biggest mistake he sees many start-ups and young companies make is to rush into commercialization, once they have received approval for their product. What they should be doing instead, is to invest in the time and resource to gather more clinical evidence to build their value proposition and also to gather intelligence on the markets they want to target.

He added though that one of the reasons why companies trip over this major snag is because they feel pressured by investors to start generating revenue and demonstrate there is a market for their product.

Speaking to Medtech Insight, Cohen said that in some cases, if you are introducing a product that is addressing a white space, in other words there is no existing market for your product yet, then you would have no choice but to go and seed the market to show investors that people do want to buy your technology and implement it into their practice.

"But if you have an established therapy that people want to buy, then you can be more judicious in picking a spot, when you want to go to market, where you want to go," he said. In addition to rushing too early into commercialization, the second biggest mistake is that people go "very wide," as opposed to deep."

"What I say is pick one market, one country, one geography, whether it's Benelux or Germany, whatever one you are most comfortable with or well positioned to do, and you go deep and you show your investors that you were able to capture X% of these physicians to buy your product in this particular market. You speak about how you can extrapolate that globally. That to me is the smart play.

When you go too wide, the only thing you prove is that, with a new product and a new market, adoption is difficult and it costs more and takes a lot longer than anybody would ever expect. And the investors then get upset, because what you've done is set certain expectations, but go out in the market and generate $1m, $2m of revenue in a wide effort but wind up spending $10m, $20m doing that. You create your own negative reality."

Cohen added that it's a "huge mistake" especially when people consider going to the US market, as that is "by far the most dangerous market in the world because it is so big and vast."

Gore's PFO Closers REDUCE Recurrent Ischemic Strokes By 77% In Trial

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Results of the REDUCE trial show **WL Gore & Associates Inc.**'s septal occluders significantly reduce the chances of recurrent ischemic stroke in patients with a patent foramen ovale – commonly known as hole in the heart – and a history of stroke compared to antiplatelet therapy alone.

REDUCE compared the efficacy and safety of PFO-closure using Gore's *Cardioform* septal occluder or the earlier generation *Helex* septal occluder plus antiplatelet drugs to antiplatelet drug therapy alone in 664 patients with a history of cryptogenic stroke at 63 sites in seven countries. After a mean follow-up of 3.4 years, the trial met its primary endpoint by showing a statistically significant 76.6% reduction in recurrent ischemic stroke in patients randomized to the PFO-closure group versus the antiplatelet medication-alone group.

There was no difference in the subject-based rate of serious adverse events between PFO-closure and control groups – 1.4% and 2.5% – and there were no significant differences in the rates of bleeding, deep vein thrombosis, or pulmonary embolism. There was a significantly higher rate of serious atrial fibrillation in the PFO-closure group than the antiplatelet group alone – 2.3% versus 0.4%, but the majority of atrial fibrillation was peri-procedural and 70% resolved within two days.

Results of the trial were presented May 16 at the European Stroke Organisation Conference in Praque by REDUCE's principal investigator, Scott Kasner of the University of Pennsylvania. "These results are very compelling and show fairly definitively that we can reduce the risk of stroke in the right population," Kasner said at the conference.

The REDUCE results "are statistically significant by [themselves] and clinically very meaningful. And particularly taken together with the CLOSE results, which are also statistically significantly positive, they suggest that we've found the population that benefits from PFO closure and that these results together are likely to be practice-changing," Kasner told *Medtech Insight*. "The stroke neurologists who were [at the ESOC meeting] were all very highly convinced by these results. Cardiologists in the US are getting this second hand, because it hasn't been presented at a cardiology meeting there yet. [But] I think the results will catch on after they're published in a good journal."

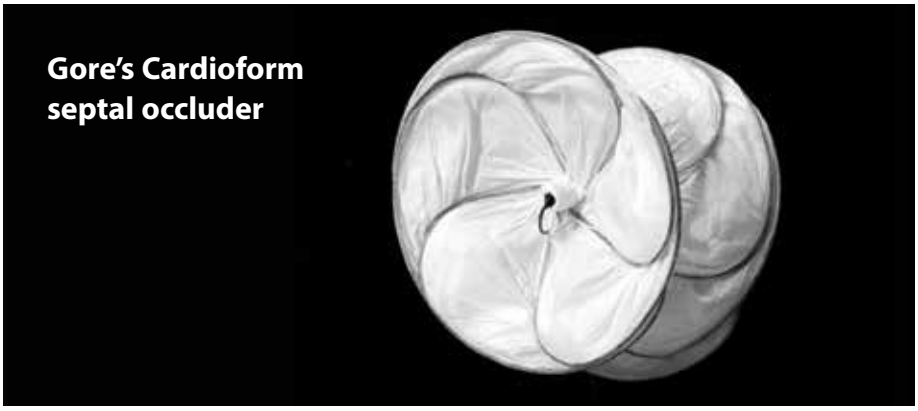

Photo credit: WL Gore & Associates Inc.

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Gore says it plans to submit these results to the US FDA to seek a PFO indication for Cardioform by the end of 2017. Cardioform is currently FDA-approved for closure of atrial septal defects, but not stroke-reduction specifically.

Cardioform is deployed via catheter intervention. The part of Cardioform that actually closes the PFO is two independent conformable discs made of Gore's proprietary, thromboresistant expanded polytetrafluoroethylene material covering a minimal wire frame. Gore says this design provides optimal apposition to the anatomy and allow tissue ingrowth for short-and long-term performance.

Also at the ESOC meeting, Jean-Louis Mas from Université Paris Descartes in France presented results of the CLOSE trial, also showed that PFO-closure plus long-term antiplatelet therapy reduced the risk of stroke in patients with a PFO and previous cryptogenic stroke compared to antiplatelet therapy alone. CLOSE also compared PFO closure and antiplatelet therapy to anticoagulant drugs, including vitamin K antagonists, rivaroxaban, dabigatran, or apixaban.

Over a mean follow-up of five years, there were 14 strokes in the antiplatelet group and zero in the group treated with a closure device, a significant 70% reduction,

Mas reported. The antiplatelet group had a 57% lower rate of strokes than the anticoagulant group, but that difference did not reach statistical significance in the trial.

GORE SUCCEEDS WHERE OTHERS FAILED BECAUSE OF PATIENT SELECTION

In most people, the foramen ovale closes soon after they are born, but in about 25% of people, this hole in the septum between the heart's atria remains open, which can allow embolisms to go directly from the right to left atria, bypassing the lungs, and going into the brain where it can cause a stroke. Several companies have tried to solve this problem with minimally invasive closure devices. After almost two decades of development, US FDA approved **St. Jude Medical Inc./Abbott Laboratories Inc.**'s *Amplatzer PFO Occluder* in October for reducing recurrent stroke in patients with a PFO and a history of stroke even though both trials supporting Amplatzer failed to show a statistically significant reduction in stroke recurrence in the primary intent-to-treat analysis. *(Also see "US Approvals Analysis: Stroke Device, IVDs Highlight October FDA Actions" - Medtech Insight, 8 Nov, 2016.)* Other companies were not as fortunate – **NMT Medical Inc.** went out of business in 2011 after its trial failed to show benefits for its *STARflex* device. *(Also see "News In Brief" - Medtech Insight, 9 May, 2011.)*

In a conversation with *Medtech Insight*, Kasner emphasized that REDUCE is the first randomized trial of a PFO closure device to show a statistically significant reduction in stroke recurrence in the primary intent-to-treat analysis.

He said that REDUCE was able to achieve the long-sought goal of stroke reduction in this population because the investigators were more careful to enroll patients whose strokes were likely due to PFO has opposed to other causes.

"Our understanding of cryptogenic stroke has evolved over the years and in REDUCE, we required that all of the patients get fairly thorough evaluations and we were a bit more stringent about this than in other trials so that should increase the likelihood that actually had their strokes due to PFO and nothing else," he said. "Other trials made some efforts at that but we may have been a big more stringent than those."

He explained that in the past when trials like the RESPECT trial of Amplatzer were run, investigators had a hard time enrolling patients with large PFOs because their doctors considered them too high risk for a randomized trial and just closed their PFO outside a trial. "But as time went on, that got harder and harder to do in the US, because with the other trials being negative and insurance companies stopped paying for PFO closure in some places. So the only options that patients had was to participate in a trial, so then we got rid of some of that selection process prior to enrollment," he said. "The fact that we included European sites where they didn't have that same pressure also improved the inclusion of a wider range of patients with appropriate cryptogenic strokes and PFOs going into the [REDUCE] trial. Of course, between-trial comparisons are challenging but those things seem plausible."

REDUCE was able to achieve the long-sought goal of stroke reduction in this population because the investigators were more careful to enroll patients whose strokes were likely due to PFO has opposed to other causes.

Kasner pointed out that most of the patients in the CLOSE trial were treated with Amplatzer, the same device that failed to achieve a statistically significant reduction in recurrent stroke in previous trials. So the success of CLOSE shows "it's not a device issue but a patient selection trial," he said.

When REDUCE was originally designed in 2006, the investigators planned to examine every patient's brain with magnetic resonance imaging at baseline and the two-year follow-up to look for "silent" brain infarctions that might not appear clinically as strokes. But after several other PFO-closure trials reported results showing that lower rates of recurrent stroke than the REDUCE investigators anticipated, they were concerned that REDUCE would not be sufficiently powered to show a difference in these clinically evident strokes.

"The idea was that clinical strokes are just the tip of the iceberg and we should see new silent brain infarctions on MRI accumulating over time on the scans of these patients and that would help to support the primary endpoint," Kasner explained. "So we elevated that to a co-primary endpoint, so one endpoints was just the clinical events and one was a composite of clinical plus MRI-events and that's novel for a trial … to say 'What is the meaning of these MRI findings?' How often do they really happen and is there a difference in the groups?'

For the composite of clinical strokes plus the ischemic events only detected on MRI, PFO-closure with a device was still associated with a 49% relative risk-reduction compared to medical therapy alone. "We didn't find a clear difference in silent events alone, but it provides an objective measure of events in an unblinded trial – which is always a criticism of these PFO-closure trials. Here's a way to objectify that," he said. "And having more events potentially gives you more efficiency in future trial designs. So if you're trying to prevent strokes with a device, this is a strategy that might be worth considering."

While both Kasner and Mas said they would definitely recommend PFO closure for younger patients who have suffered a cryptogenic stroke, the long-term safety of these devices beyond about five years is not yet known. For example, Amplatzer has caused septal tissue erosion in some rare cases, he noted. So long-term follow-up is needed to understand the significance of those risks.

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Endologix Joins Gender-Specific Movement To Target Women

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The early success of **Endologix Inc.**'s *Ovation* endovascular abdominal aortic aneurysm (AAA) stent graft in the LUCY trial is a milestone for the ongoing effort by industry, researchers, and the FDA to better understand and address gender-specific challenges to cardiovascular device therapies.

LUCY study is a prospective non-randomized post-market registry designed to evaluate the low-profile (14 French) Ovation, which Endologix acquired in the 2016 deal for **TriVascular Technologies Inc.**, specifically in women. The trial enrolled 225 patients, including 76 females in the treatment group and 149 males in the control group, at 39 US sites. The primary endpoint is the 30-day major adverse event rate, but one-year follow-up data will be shared later, according to the company.

The 30-day follow-up results from the 225-patient LUCY trial, announced May 31, showed that at least 28% more women would be eligible for AAA repair with Ovation than other AAA stent grafts. So far, the procedural success rate has been 100% and the major adverse event rate in women is 1.3%, which is lower than that reported in other endovascular aneurysm repair (EVAR) registries. So far, there have been no deaths, no proximal endoleaks, no limb occlusions, and a low hospital readmission rate of 3.9% for the women in the trial, the company reports.

A recently published metaanalysis sponsored by the UK's National Institute for Health Research showed that women are less likely than men to be eligible for EVAR due to anatomical challenges and that women are less likely than men to be offered intervention, while women in need of AAA repair have a higher operative mortality than men with either endovascular or open surgical AAA repair. Data collected by the National Surgical Quality Improvement Program shows that women are at higher risk for 30-day death and major complications after an intact AAA repair and that some of this disparity with outcomes in men can be explained by differences in women's aortic size.

However, LUCY has not shown increased morbidity and mortality in women, study co-chair Venita Chandra of the Stanford School of Medicine told *Medtech Insight*. "[EVAR] is one of the biggest technological breakthroughs in vascular surgery and has had significant impact on morbidity and mortality, but we didn't see as much of a significant impact on women," Chandra said. "Women have smaller access vessels and more complex aneurysmal anatomies so you really need to look at whether or not the healthy part of the aorta under the renal arteries looks like and the shape of that. The straighter and the longer or the healthier that is, the better the chance you have of success with EVAR, but in women you more commonly have shorter and more angulated necks and that makes it more difficult for traditional EVAR devices."

Chandra said Ovation is especially suitable for women because of its ultra-low profile and its overall conformability "made it deal with the more complex challenging [aortic] necks a little better." She said the key to the Ovation technology is the unique cross-linking polymer which the interventionalist injects perioperatively to inflate the endograft envelop so that the sealing ring conforms to the aortic wall. "A lot of other companies have tried to make low-profile [EVAR] technologies. Unfortunately, we've found that some of them have trouble - the primary thing is that you have to thin everything to make it small enough to get through these smaller vessels. There's limb occlusion and limb-kinking issues with some of the technology. You definitely need to make it smaller but you have to make sure it's still durable," Chandra said.

Chandra said that the significance of the LUCY results go far beyond the development of a single device that performs especially well in women. "Besides the fact that we're basically focusing on a subgroup of the population that nobody has focused on before, I think that now we can potentially answer a lot of questions related to female aneurysmal anatomy and get a little better understanding of why they're so different. The differences in terms of their anatomy are not just explained by 'women are smaller than men.' There's something else. The pathophysiology is different," Chandra said.

"Having this repertoire of data and being able to some analyses and show dynamic modeling with this data would … help us better understand the differences that we see between [male and female aortic] anatomy," she said. "We know other things too - women's aneurysms grow faster, they rupture at a smaller rate, so we just don't have all the answers yet, so it's really exciting to look at those other questions with this data."

BOSTON SCIENTIFIC CONTINUES EFFORT TO WIN MORE FEMALE TRIAL SUBJECTS

US FDA and other stakeholders have been actively trying to get more women, and a more diverse population of women, to enroll

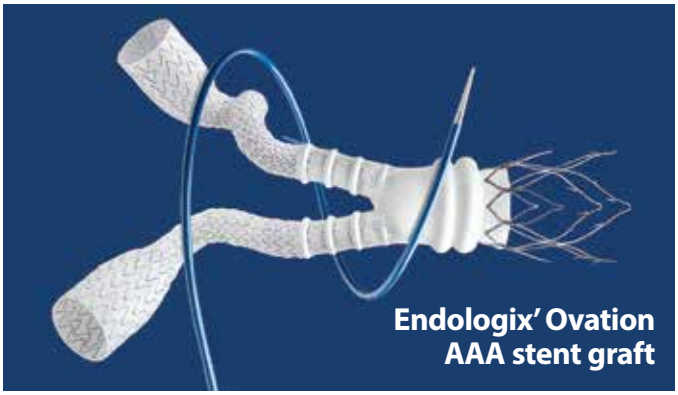

Photo credit: Endologix, Inc.

"Women have told us that they need more information on average than male patients. They likely don't want to make a decision during the initial conversation."
– Brooke Allocco, Boston Scientific

in clinical trials for more than 20 years, and Congress established the agency's Office of Women's Health in 1994 to advocate for the participation of women in clinical trials and encourage gender-specific analyses of clinical trial results. *(Also see "CLINICAL CORNER: Boston Scientific Wants More Women In Trials, Abbott's Absorb FDA Panel Date Set, InVivo And Edwards Get Clinical Plans Nod; MiMedx; MDxHealth" - Medtech Insight, 21 Jan, 2016.)*.

The MADIT S-ICD study comparing **Boston Scientific Corp.**'s *Emblem MRI S-ICD* to conventional medical therapy in patients with a prior myocardial infarction, diabetes, and a relatively preserved ejection fraction of 36-50% began enrolling patients this spring. *(Also see "HRS 2017: Medtronic And Boston Scientific's Less-Invasive CRM Devices Perform As Hoped In Real-World Registries" - Medtech Insight, 14 May, 2017.)* While announcing the start of MADIT S-ICD, the company said it will be part of the WIN-Her (Women Opt-In for Heart Research) program, launched in 2016 to ensure adequate representation of women in clinical trials.

WIN-Her is also working with the ASAP TOO trial, which is evaluating Boston Scientific's *Watchman* left atrial appendage closure device in patients with non-valvular atrial fibrillation who are deemed not to be eligible for anti-coagulation therapy. *(Also see "Starts & Stops: Boston Scientific Starts, Stops, And Finishes TAVR Trials" - Medtech Insight, 14 Mar, 2017.)* Cardiologists Jeanne Poole of the University of Washington in Seattle and Marye Gleva at Washington University in St Louis are the physician leads for the initiative.

"The goal of the program is really to understand how we can overcome barriers to female enrollment in trials of cardiovascular devices, and then how we can increase the number of women that we enroll and study in our trials," Brooke Allocco, Boston Scientific's VP of Clinical Communications, told *Medtech Insight*. "Cardiovascular disease can present differently in women and they may respond differently to therapy and women have been historically underrepresented in clinical trials of cardiovascular therapy and we hope to change that with this initiative."

She pointed out that, contrary to a common assumption among non-statisticians, "enough women" in a trial does not mean half of the trial participants must be women. It means that there must be enough women in the trial so that it has enough statistical power to answer gender-specific questions about the therapy. But often, especially in cardiovascular device trials, not enough women are in the trial to determine if women are likely to present special challenges to the therapy or have outcomes different than men's'.

Allocco said her company's research has discovered that women are frequently not be aware that they have an opportunity to participate in a trial, either because their local center is not participating or nobody has approached them about participating. And of those who are approached to participate, some women "may not have a good conversation about participation with the investigational site and so they may not understand the risks or benefits of participating," Allocco said. "I understand that participation may be intimidated by the thought of being a guinea pig or an experimental subject." Meanwhile, some women may not be able to participate due to or logistical challenges relating to transportation or family responsibilities.

"We need to make more women aware of the opportunities to participate [and] we need to make sure that we have appropriate education material that will dispel any misperceptions or unnecessary concerns that female patients have," Allocco said.

Boston Scientific is enhancing its patient-education material to "communicate to patients about these trials in language that they can understand and with the level of detail that they need to feel comfortable making a decision," she said. "We're training our physician investigators and research coordinators to have different and more effective conversations with patients around trial participation."

Allocco said the company is also encouraging investigators to give patients more time to make their decision about participating in a clinical trial and paying investigators for the extra time it takes to have thorough discussions with patients about participating in a clinical trial. "Women have told us that they need more information on average than male patients. They likely don't want to make a decision during the initial conversation." WIN-Her is also tracking enrollment metrics and tracking why patients chose to participate or not participate in a clinical trial.

"We won't solve everything with this first project, but we hope that this can significantly grow the knowledge base around this topic. We [also] know that we won't solve it ourselves as industry, but that solving this challenge requires partnership among multiple stakeholders, including physician investigator industry and the FDA," she said. "Our hope is that with the learnings from this that we can continue to work with FDA and other stakeholders to influence the dialogue to influence the direction on this topic."

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