New Device-Failure Database Benefits Companies And Savvy Consumers, But May Befuddle Others, Experts Say

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Device-makers and industry-savvy consumers will discover a bevy of useful information in a new international database of product recalls and safety notices, but the public repository could prove confusing for laypeople, experts say.

The International Medical Devices Database (IMDD) from the International Consortium of Investigative Journalists is an output of ICIJ’s recent string of “Implant Files” stories that were critical of industry. In its Implant Files series, ICIJ makes the case that patient safety is being compromised in countries throughout the world, with insufficient tracking of adverse events and recalls, and companies putting profits before safety. More than 250 journalists worked on the yearlong investigation.

Found at https://medicaldevices.icij.org, the IMDD includes information on device recalls, field safety notices and safety alerts documented in 11 countries: the US, Canada, Mexico, Switzerland, Spain, Australia, Finland, Lebanon, the Netherlands, India and Peru. ICIJ will add data from more countries as it becomes available.

"To be able to look at data on competitors is a huge plus, because right now, extracting that type of information ... is extremely challenging," consultant Ricki Chase says.

There are more than 700,000 events stored in the database, says ICIJ, which collected the data from public sources and FOIA requests. FOIA is the United States' Freedom of Information Act. ICIJ said it made the repository "in the public interest to provide vital safety alerts and potential recourse to patients who, in most parts of the world, have been shut out from such information until now" – but that doesn’t mean device manufacturers can’t use data in the IMDD to their advantage. Ricki Chase, a compliance practice

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Meddevicetracker: Medical Device Intelligence and Forecasts

Stay up-to-date and get a complete view of the continually evolving medtech landscape with access to real-time market intelligence on product and company developments across the medical devices, diagnostics and advanced delivery systems markets.

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Inside:

Cover / New Device-Failure Database Benefits Companies And Savvy Consumers, But May Befuddle Others, Experts Say – The International Medical Devices Database from the International Consortium of Investigative Journalists offers information on more than 700,000 device recalls, field safety notices and safety alerts documented in 11 countries. Device-makers and shrewd consumers will discover a bevy of useful data in the public repository, but it could prove confusing for laypeople. A recalls expert and an ex-FDA official weigh in.

Editors' Picks

5 An FDA Age-Based Predicate Policy Would Be Arbitrary, Reg Experts Complain – The device industry is still sorting out the implications of US FDA's recent proposals to make a major update to the 510(k) process. But regulatory experts say the agency's focus on finding an age-based cutoff for 510(k) predicate devices is misguided, and some argue that Congress should need to sign off on any of the floated policies.

6 Apollo And ReShape Swap Bariatric Devices – Apollo Endosurgery sold its surgical product line, including the Lap-Band adjustable gastric banding system and other accessories for laparoscopic bariatric surgery, to ReShape Lifesciences for $17m plus other considerations, including rights to the ReShape endoscopic balloon.

Commercial

7 Boston Scientific Makes A Move In Mitral Valve, Sealing $325M Deal With Millipede – Boston Scientific has acquired the remaining shares of privately held mitral-valve repair device company Millipede for $325m.

8 Mobidiag Forms Joint Venture With Autobio – Finnish molecular diagnostics company Mobidiag is partnering with Chinese company Autobio Diagnostics in a new joint venture to commercialize its Novodia platform for infectious disease diagnostics.

8 CarThera Secures First VC Investment To Run Pivotal Study Of Glioblastoma Therapy – CarThera has secured its first financial round from institutional investors to launch a pivotal trial evaluating the company's Sonocloud ultrasound therapy for patients with recurrent glioblastoma.

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Exclusive Online Content

MedTech Europe on the "Implant Files"

Weeks after the "Implant Files" journalistic investigation of the medical device industry was released, EU industry advocate Serge Bernasconi described the results as “unhelpful” and “imbalanced.” But he said in an interview that his group, MedTech Europe, and the journalists have the same goal: safer products.

Safety Signals
https://bit.ly/2R5vet1

In recent weeks, US FDA called a meeting to further explore safety risks for surgical mesh devices and ordered Bayer to extend its post-market study of the troubled birth-control device Essure.

Smart Glove And Gaming For Stroke

After making its Korean IPO debut, Korean-American medtech start-up Neofect Inc. hopes to bring its gamified rehabilitation solutions to more stroke and spinal injury patients in the US. Medtech Insight profiles the firm.

FDA/CMS Summit Podcast
https://bit.ly/2QjxU0H

Medtech Insight sat down with conference organizers to talk about some of the overarching themes and issues discussed at the recent FDA/CMS Summit in Washington, DC.

Device Week

Medtech Insight journalists talk about 2018 merger and acquisition trends and highlights in the latest episode of our weekly podcast. Also check out our recent episode discussing the top US legal issues for device and diagnostics firms in 2018.

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9 Meeting Planned To Discuss Drug-Eluting Device Death Risk – Two trials of paclitaxel-coated devices to treat peripheral arterial disease have been halted in recent weeks due to reports the devices carry a higher mortality risk. Endovascular physician group VIVA is organizing a February meeting to discuss the issue.

10 Start-Up Spotlight: Small Lens In Eardrum Hopes To Make Big Soundwaves In Hearing Aid Market – A new hearing aid lets users enjoy the full range of normal hearing frequencies, activated by a "contact lens" on the eardrum. The hearing aid from Earlens Corp. also provides audio gain without feedback.

12 WashU Researchers Plan Major Trial Of Noninvasive Radiation Ablation For Ventricular Tachycardia – Physicians developing a promising technique for noninvasive cardiac radioablation for ventricular tachycardia are working with US FDA to develop a large trial to evaluate the approach following the success of a five-patient case-series and an 18-patient prospective study.

LEGAL ISSUES

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15 UK Into 2019: Health-Tech Adoption Not Far From The "Tipping Point" – The UK’s future economic relationship with the EU consumed more than its fair share of headlines in 2018. But within UK health care, Brexit was often missing entirely from main conference agendas, as stakeholders sought to both maximize current operating conditions and prepare for future health-care architectures and evolving innovation systems.

POLICY & REGULATION

18 Breakthrough Pathway Final Guidance Eases Sponsor-Regulator Interaction Requirements – US FDA issued a final guidance that sets out requirements for its new Breakthrough Devices Program mandated by Congress. Under the new program, which replaces the Expedited Access Pathway, sponsors have more certainty about how quickly they will get responses from the agency and fewer requirements when setting up early interactions.

19 FDA Marches Forward With "STeP" Program To Aid Development Of Significantly Safer Medtech Products – The US agency is planning to launch another accelerated device approval program along the lines of its successful Breakthrough Devices Program. But this one, the Safer Technology Program (STeP), would focus on devices with enhanced safety features.
An FDA Age-Based Predicate Policy Would Be Arbitrary, Reg Experts Complain

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There are still many details to be worked out with US FDA's plans to reform the 510(k) process, but expert observers suggest the agency's focus on favoring newer predicates may result in arbitrary policies.

The agency floated reform proposals last month, including the possibility of publishing a list of all cleared devices that had been based on predicates more than a decade old as a means to encourage companies to adopt new predicates to support 510(k) devices. (Also see "Nudging Firms To Ditch Older Predicates: A Step In US FDA's Planned 510(k) Reforms" - Medtech Insight, 26 Nov, 2018.) FDA also said it was considering policies to more formally "sunset certain older predicates and promote the use of more modern predicates," as it also moves toward finalizing an alternative 510(k) pathway that relies on performance criteria rather than device-to-device comparisons.

FDA's emphasis on the age of a predicate may be misguided, several attorneys and medtech regulatory experts suggest, pointing out that there is not a generally applicable cut-off for when a predicate can be considered too old.

The agency makes clear that it is not arguing that a device cleared based on a predicate that is more than 10 years old is inherently unsafe. But, it argues, the fact that nearly 20 percent of current 510(k)s are cleared based on a predicate that's more than a decade old "does mean that some devices may not be continually improving, which is the hallmark of health technologies."

"Coming up with an arbitrary 10-year rule, for a predicate, I am not sure what the basis for that is," said Christy Foreman, a senior consultant with Biologics Consulting and former director of FDA's Office of Device Evaluation. "With the predicate system, it is really hard to say, 'why is a predicate from 11 years ago bad and a predicate from 9 years ago good?' Some devices are evolutionarily stable, such as endotracheal tubes, where the age of the predicate is likely not significant. But in devices areas with high rates of change such as software and artificial intelligence, it may be more meaningful. It just seems arbitrary without truly addressing what the concern might be."

Quynh Hoang and Elaine Tseng, medical device regulatory experts with law firm King & Spalding, agreed, in a joint written response to Medtech Insight’s questions, that the focus on an age-based cut-off will not necessarily address FDA's concerns.

The agency’s stated reasoning to ensure devices meet current standards for cybersecurity, interoperability, biocompatibility and usability engineering could be problematic, suggest Hoang and Tseng.

"FDA should consider the reasonability of applying a bright-line rule for the age of predicates to other devices for which the referenced standards are not applicable, or where predicates, notwithstanding their age, may still represent the current state of technology,” they said. “As the agency seems to acknowledge, setting an appropriate bright-line age (e.g., the Agency proposes 10 years as a starting point for consideration) to define ‘older’ predicates may be difficult as a general matter.”

Observers who spoke to Medtech Insight noted several legitimate reasons why manufacturers may look to an older predicate. For example, some simple devices may not require much innovation; in other cases, a new 510(k) might improve on less expensive technology used in an older predicate, or sponsors may need to use an older predicate to match a specific intended use.

Bradley Merrill Thompson, an attorney with Epstein Becker & Green, argued that FDA hasn’t established that devices using predicates more than 10 years old are less safe as a group than those with newer predicates.

"The selection of a predicate is a very important decision, but only in the sense that there must be a predicate," he said. "Beyond the existence of a predicate, submissions must demonstrate compliance to any special controls FDA has adopted.”

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Apollo And ReShape Swap Bariatric Devices

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eShape Lifesciences Inc. has acquired the Lap-Band adjustable gastric band surgery system from Apollo Endosurgery Inc. in exchange for $17m and the ReShape Balloon intra-gastric bariatric product line, the companies announced Dec. 18.

In addition to the product-swap, ReShape has agreed to pay Apollo $17m, including $10m paid at closing and $7m to be paid in three annual installments. The companies signed and closed the definitive transaction agreements simultaneously on Dec. 17.

Apollo says it is selling Lap-Band so it can focus resources on its Endo-bariatric product offerings, including the OverStitch endoscopic suturing systems and the Orbera intra-gastric balloon to treat obesity.

"Our surgical product line has served an important purpose for us, but it is no longer a strategic fit with our focus on our Endo-bariatric products and therapies," Apollo CEO Todd Newton says in a release. "We also remain very bullish on the potential of the intra-gastric balloon market. We believe it is in the best interest of Apollo's customers and shareholders that we direct our attention exclusively to the growth opportunities being afforded to us from these products."

Apollo acquired both Obera and Lap-Band from Allergan in 2013 for $110m in up-front and milestone payments (Also see “Al-lergan trims off fat-busting portfolio to Apollo” - Medtech Insight, 30 Oct, 2013.)

Apollo is acquiring the ReShape intra-gastric balloon even though it does not fit into its long-term plans.

"While the ReShape intra-gastric balloon will remain available for the near term, Apollo intends to focus its commercial efforts exclusively on its Orbera intra-gastric balloon products," the company says in the release announcing the deal. Apollo noted it will use the $10m upfront cash proceeds from ReShape to pay down debt.

Lap-Band has been a drag on Apollo's revenue growth in recent years. On Nov. 8, the company reported that its total surgical product sales decreased 34% year-over-year, in the third quarter of 2018, and 32% for the first nine months of 2018, because of reductions in gastric banding procedures being performed worldwide.

Apollo's intra-gastric balloon revenues were hit hard by US FDA labeling changes for both the Orbera and ReShape, announced June 4.

The new labeling includes new mortality statistics, as well as more information on how to manage patients experiencing side effects. FDA says the death rate is 0.06% with the ReShape device and below 0.01% for Orbera, but 12 deaths linked to the devices have been reported since 2016. The June 4 letter added seven deaths to the total recorded in FDA's Aug. 2017 letter to physicians.(Also see “Gastric Balloon Labeling Updated After Patient Deaths” - Medtech Insight, 5 Jun, 2018.)

Sales of Apollo's intra-gastric balloon products weredown 7.7% in the third quarter and 3.8% in the first nine months. But, during a Nov. 8 earnings call, Newton said, "We continue to be bullish on Orbera." He pointed out that sales of Orbera recovered about four months after FDA's August 2017 letter, "and it appears it will take about the same time to work past the effect of the FDA's June letter too."

"Because Orbera is a cash pay procedure here in the United States, our business today is very consumer-driven and can be heavily influenced by media impressions, either positive or negative," he said. "Since the June FDA letter, which generated negative media impressions, we and our largest Orbera customers have continued to be engaged in consumer education and marketing."

LAP-BAND BRINGS RESHAPE CLOSER TO BREAK-EVEN

ResShape’s CEO and chairman of the board, Dan Gladney, explained the rational for the deal from ReShape's perspective during a Dec. 18 conference call.

"This transaction is a meaningful and positive move for ReShape Lifesciences as we continue to refine our strategy to be a comprehensive provider of patient-friendly, not-anatomy-altering solutions for obesity and metabolic diseases," Gladney said in a release.

Lap-Band gives ReShape an immediate opportunity to improve its bottom line and move closer to profitability.

For the first nine months of 2018, ended Sept. 30, ReShape reported total revenue of $1.95m and a net loss of $53.5m. In a Nov. 28 financing and corporate update, ReShape said it has enough capital to fund its operations through 2020, but would need an another $60m to $70m in funding to get to “break-even.”

During the Dec. 18 earnings call, Gladney said that adding Lap-Band - which is FDA-approved and currently reimbursed by most private payers in the US - will rapidly reduce this gap to $30m to $40m.

"The required investment in Lap-Band is minimal, particularly compared to the investment in marketing and sales that would
have been required to get the balloon-product line to become a meaningful contributor to ReShape," he said. "As such, the swap of these assets leads to significantly reduced cash requirements to get ReShape Lifesciences to cash-flow positive."

Lap-Band complements ReShape’s vBloc minimally invasive neuromodulation therapy, because both devices are usually provided by bariatric surgeons, Gladney said. The company also expects bariatric surgeons to be the "core customers" for the ReShape Vest, which is about to enter trials in Europe. (Also see "EnteroMedics Inflates Neuromod-Obesity Offering With ReShape Balloon" - Medtech Insight, 4 Oct, 2017.)

ReShape Vest is a laparoscopically implanted medical device that wraps around the stomach, emulating the gastric volume reduction of conventional weight-loss surgery without permanently changing patient anatomy.

"The bariatric surgeon community is where we have the longest-standing and deepest relationships," Gladney said.

ReShape is optimistic about Lap-Band’s market potential, even though its sales have been declining in recent years. "Revenues from the Lap-Band product under Apollo's ownership have been a bit unstable, [because] Apollo has chosen to put limited resources behind the product," Gladney said. But even "with this small effort, Apollo's Lap-Band revenues were $14.6m in the first nine-months of 2018 and generated high-gross margins. "With an effort from our team, we can level-off the declining revenues and enjoy a solid contribution from this very profitable product."

Lap-Band also gives ReShape an entrée into the US market, and a distribution system outside the US. "This will save us time and money once the Vest is approved," Gladney said.

ReShape Lifesciences was known as EnteroMedics until Oct. 2017, shortly after EnteroMedics acquired privately held ReShape Medical for cash and stock. (Also see "EnteroMedics Inflates Neuromod-Obesity Offering With ReShape Balloon" - Medtech Insight, 4 Oct, 2017.)

Cardiovascular giant Boston Scientific Corp. has inked a $325m deal to acquire the remaining shares of California start-up Millipede Inc.

Santa Rosa-based Millipede is the developer of the IRIS Transcatheter Annuloplasty Ring System for the treatment of patients with severe mitral regurgitation (MR) in which blood flows backward in the heart through a leaky mitral valve. The condition can lead to heart failure, abnormal heart rhythm, high blood pressure and other problems.

Boston Scientific said it decided to acquire the remaining shares of Millipede following the successful completion of its first-in-human clinical study. Boston Scientific initially entered into an investment and acquisition option agreement with Millipede in January 2018. (Also see "Boston Scientific Hooks In Millipede, But Still Trailing Behind In Mitral Valve Race" - , 25 Jan, 2018.) The company purchased $90m in existing and newly-issued Millipede shares, with the option to acquire the company’s remaining shares for $325m at closing, with a $125m payment available based on achievement of a commercial milestone.

The deal expands Boston Scientific’s Structural Heart portfolio and places the company’s foot in the mitral valve door. The transcatheter mitral repair and replacement market is estimated to reach $1bn by 2021, with the majority comprised of repair procedures. However, Boston Scientific is some distance behind it’s cardiovascular rivals in the space. Edwards Lifesciences Corp. has invested in several mitral valve technologies that have advanced further down the clinical and commercial path compared to rivals like Millipede. In January 2017 the company acquired a similar technology to Millipede’s IRIS called Cardioband, which was CE marked in September 2015. Edwards is running a US pivotal trial for Cardioband and estimates US FDA approval in 2020.

"Upon commercialization, we believe the IRIS system can meet the needs of a currently underserved patient population that requires physiological, less invasive options to treat functional mitral regurgitation in patients with progressive heart failure," said Ian Meredith, executive VP and global chief medical officer for Boston Scientific. "This device is designed to be highly customizable to a specific patient’s mitral anatomy and disease state and is repositionable and retrievable to promote a high-quality outcome."

Boston Scientific said it expects the deal to be dilutive to its earnings per share for each of the next several years; all dilutive impacts are expected to be absorbed via internal trade-offs, with no net adjusted EPS impact. The acquisition is due to close in Q1 2019.

Boston Scientific Makes A Move In Mitral Valve, Sealing $325M Deal With Millipede

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### Mobidiag Forms Joint Venture With Autobio

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tland-based Mobidiag Ltd. is teaming with Chinese company Autobio Diagnostics to commercialize its molecular testing platform for infectious diseases.

Founded in 2000, Mobidiag has two product lines on the market – Amplidiag and Novodiag. Amplidiag is a family of diagnostic tests for high-volume screening of gastrointestinal pathogens and antibiotic resistances and Novodiag is an automated platform for screening infectious diseases, including antibiotic resistance. The system utilizes real-time PCR and microarray technologies to analyze samples placed in a disposable cartridge, with results produced within one hour.

Under the terms of the agreement, Mobidiag and Autobio will jointly invest €12.3m to establish a company in China to commercialize the Novodiag platform. Autobio will invest €8m in cash to hold 65%, and Mobidiag will invest €4.3m to hold 35% of the joint venture, which will register Novodiag with the Chinese regulatory authorities and hold exclusive licenses for three infectious diseases assays. It will also finance local facilities to manufacture some Novodiag components and disposables within the country.

Mobidiag said the affordability of its products give the company a competitive advantage on the market. "The joint-venture has been set up specifically to commercialize the Novodiag platform in China - where there is a great need for rapid, accurate and low-cost diagnostics for infectious disease," Mobidiag CEO Tuomas Tenkanen told *Medtech Insight*. "Autobio Diagnostics is an established leader in diagnostics in China which makes them an ideal partner. We are confident that their unparalleled access to the rapidly growing Chinese market combined with Mobidiag's deep expertise in molecular diagnostics will result in a successful partnership that will bring syndromic diagnostic panels to China at an affordable price."

In addition to establishing the joint venture, Mobidiag has received a €10m equity investment from Autobio to grow its portfolio. "We plan to accelerate the development of further assays for the Novodiag system and enhance manufacturing capabilities," Tenkanen said. "As well as continuing to facilitate Mobidiag's existing commercial expansion through direct sales and through distribution partners."

Donald Xu, managing partner of Lynx Financial, which served as the financial adviser for the agreement said the deal epitomized a current trend in cross-border transactions in the healthcare sectors between China and western countries. "The strategy of combining investment with joint venture, will be the playbook for many upcoming and innovative companies to catapult their regulatory and commercialization process, and to compete against the entrenched multinationals, not only in China market, but also the rest of the world," Xu said.

### CarThera Secures First VC Investment To Run Pivotal Study Of Glioblastoma Therapy

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ench device-developer CarThera has secured €9m (US$10.3m) to develop *SonoCloud*, an ultrasound technology designed to make the blood-brain barrier more permeable and increase penetration of drugs into the brain to improve treatments for patients with brain tumors and neurodegenerative diseases.

The $10m is the first financial backing the company has received from institutional investors and marks a key milestone in the company’s progression, CarThera CEO Frédéric Sottilin, told *Medtech Insight*. The proceeds of the Series B round will be used to launch a pivotal trial of SonoCloud in France and the US in patients with recurrent glioblastoma. The company also has on-going clinical study in France for patients with Alzheimer’s disease and one planned for patients with brain metastases.

The walls of the blood vessels in the brain are impossible to cross for certain molecules. This barrier limits neuronal exposure to toxic agents, but can also be an obstacle for therapeutic drugs. CarThera’s device is implanted into the skull of the patient and activated prior to injection of a therapeutic agent. Several minutes of
Meeting Planned To Discuss Drug-Eluting Device Death Risk

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With concern over drug-eluting stents growing after a meta-analysis found a risk of patient death, two studies have been cancelled and a physician group has announced that a conference to discuss the issue is in the works.

The meta-analysis, published Dec. 6 in the *Journal of the American Heart Association*, reviewed data from 28 studies comparing outcomes for peripheral arterial disease (PAD) treated with paclitaxel-coated balloons or stents with untreated balloon therapy.

The researchers, led by Dr. Konstantinos Katsanos of Patros University Hospital in Rion, Greece, found that the patient groups had a similar mortality rate at one year. However, there was a 68% increase in deaths from all causes in patients treated with the drug-eluting devices at two years, and a 93% increase at five years. After five years, 14.7% of patients treated with drug-eluting stents died, as opposed to 8.1% of patients in the control group.

The death risk appeared to be higher for devices that included higher doses of paclitaxel, the study said.

Since the study was published, researchers in Sweden and the UK have suspended three trials that used drug-eluting balloons to treat PAD. Sweden’s Sahlgrenska University Hospital suspended SWEDGEPAD 1 and 2, while the University of Birmingham announced it was pausing recruitment for its BASIL-3 study.

“Whilst the population of the reviewed trials differs from those in the BASIL-3 trial, it is clearly important new information that may cause concerns for the BASIL-3 trial in relation to patient safety," the Birmingham researchers said in a statement.

“As such, it raises the need to consider whether changes to the trial protocol and patient information are required. We have therefore decided to suspend recruitment to the trial, pending further discussions.”

The statement asks participants to continue to follow enrolled patients per the protocol, but not to enroll new patients.

Similarly, SWEDGEPAD researchers said they spoke with the project’s data safety monitoring committee and agreed to pause enrollment in SWEDGEPAD 1 and SWEDGEPAD 2. The studies were looking at amputation rates and quality of life for patients with PAD.

Vascular InterVentional Advances (VIVA) Physicians announced Dec. 14 that the nonprofit will sponsor a 1.5-day meeting to discuss the efficacy and safety of minimally invasive, catheter-based interventions to treat peripheral artery disease, such as drug-eluting devices. The group is inviting experts in peripheral vascular intervention, as well as representatives from medical societies, the commercial medical device sector, US regulatory and reimbursement agencies, and patient advocates.

The meeting is planned for Washington, DC, in February, with an exact date and location yet to be announced.

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START-UP SPOTLIGHT:
Small Lens In Eardrum Hopes To Make Big Soundwaves In Hearing Aid Market

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While conventional hearing aids achieve limited improvement for age-related hearing loss and often have drawbacks, EarLens Corp. said its system can help users listen more broadly and with less interference.

Better listening, however, has its price.

“We are focused on the medical model, which is the ENT and the audiologist,” EarLens’ president and CEO Bill Facteau told Medtech Insight. “But our hearing aid is also high-end, at a retail price of $12,000 for one pair, so it is not for everyone.”

Given that 14% to 15% of the population worldwide is affected by age-related hearing loss, also known as sensorineural hearing impairment, which translates into a $6bn annual market, Facteau said there’s plenty of ears to still hear about EarLens (see photo below, courtesy of EarLens.)

The hearing aid received US FDA 510(k) clearance in September 2015 for use in adults with mild to severe sensorineural hearing impairment. The FDA reviewed the device through a de novo pathway. The company’s device also received the CE mark in February 2015.

“Penetrating just one percent of the market, which we realistically expect to do within the next five years, makes a really compelling, successful business,” Facteau said.

Earlens is different from conventional hearing aids in several ways.

For one, it doesn’t use a tiny speaker to direct amplified sound in the ear canal, which provides restricted frequency bandwidth with a peak output and has the risk of “whistling” acoustic feedback.

Traditional hearing aids also only provide audibility improvements over a narrow frequency range, roughly 800 to 5,000, which compares to 100 to 10,000 hertz for normal adult hearing.

The Earlens system doesn’t have a speaker, rendering essentially a silent hearing aid.

The device allows for normal, adult full-frequency range and a more natural and clearer amplification. It uses a laser light tip that’s placed in the ear canal to transmit data and energy directly to the custom contact lens, sitting in the eardrum.

The contact lens, made of a variation of Chronosil plastic (AdVanSource Biomaterials), is comparable to the size and weight of an aspirin tablet.

After sound is transmitted by laser to the photodetector on the lens, the motor contained within the lens assembly drives the first bone of the middle ear through very fine movements -- from a minimum movement of less than the diameter of a hydrogen atom to a maximum movement of one-fifth the diameter of a human hair.

“The laser shines the light onto basically a solar panel, which is part of the contact lens,” Facteau explained. “The contact lens receives the data and energy encoded in the laser signal to drive the ear bones for natural hearing. Additionally, we are able to attain significant audio gain without feedback, because we don’t have a speaker/microphone feedback loop like a typical air conduction hearing aid.”
Earlens has 138 issued or pending global patents and does not share royalties and/or revenues with another entity.

The company had a limited launch in the US in 2017, which Facteau said, was positive. “Our hearing aid has been well received,” he said.

He hopes, however, to make a bigger splash on the market with an upgrade, pending 510(k) clearance from the FDA.

The hearing aid is dispensed in concert by an ENT and audiologist.

First, the ENT takes an impression of the patient’s complete ear canal and tympanic membrane, which is then shipped to the company where the molds are digitally scanned and parts are custom-modeled for each patient using advanced 3D printing technology.

The contact lens is then sent to the ENT within about two weeks after initial molding. The physician uses a microscope and basic tools to fit the lens on the patient’s ear in an office setting with no anesthesia, akin to placing a contact lens on the eye.

After receiving the photon processor (in one of four colors) and custom light tip, the audiologist personalizes the programming and positions the processor behind the ear; he then places the light tip, which resembles a custom earbud, in the ear canal.

“The only visual is the traditional hearing aid that sits behind the ear,” Facteau said.

The patient removes the photon processor, which contains a rechargeable battery, at night to recharge. But the lens stays on the ear at all times, including while showering or swimming.

Within the trial period of the first 70 days, there are four or five office visits total. The patient returns to the audiologist for any fine-tuning of sound quality, while issues of ear, wax and the lens are referred to the ENT.

The hearing aid comes with a three-year warranty; however, patients have the option of purchasing an extended warranty out to five years.

“Generally, people update their hearing aid once every four to five years,” Facteau said.

FULL SPECTRUM

Charles Syms, an otologist and neurotologist in private practice in San Antonio, Texas, has dispensed about 40 pairs of Earlens hearing aids over the past two years. He praises the technology.

“This hearing aid provides hearing in the higher frequencies that are currently not available with any other nonsurgical technology,” Syms told Medtech Insight. “You achieve the full spectrum of sound, from the lows to the highs; particularly the high frequencies, which are not well served by acoustic hearing aids.”

Syms’ ideal candidate for the Earlens hearing aid is one who meets the fitting criteria (from mild to severe hearing impairment) and/or is an experienced hearing-aid user.

“Patient feedback has been extremely positive,” Syms said. “Sound is closer to what they experienced before their hearing loss, without the compromises of the acoustic hearing aids.”

The new technology is most apropos to patients who are frustrated with their current hearing devices.

“I also think the Earlens hearing aid will go all the way up to displacing some patients who are currently candidates for cochlear implants, because there is no surgery involved,” he said.

The greatest drawback to the Earlens hearing aid, though, compared to conventional hearing aids, is the initial commitment of time required by patients to be fitted and properly programmed, according to Syms.

Earlens has published roughly a dozen clinical studies about its hearing aid, which show that high-frequency performance and full bandwidth are superior to conventional hearing aids, and demonstrate the safety and efficacy of the lens. Over time, patient satisfaction for sound quality has also increased, especially while listening to music.

“Patients appreciate the ability of our hearing aid to deliver a wide range of frequencies,” Facteau said.

COMPETITIVE LANDSCAPE

The top three companies in the hearing aid space are Phonak (part of Sonova Holding AG), GN ReSound and Oticon Inc.

“They all use the same underlying mechanism of action, which is a speaker directing sound into the ear canal,” Facteau said. “And they all have the same limitations associated with the speaker: restricted bandwidth, limited output and a propensity for feedback. Many of our studies show a preference of our hearing aid over those of competitors.”

Rodney Perkins, a prominent otologist and a serial entrepreneur in the medical device space from Woodside, California, founded Earlens in 2005. He also founded the giant hearing aid company ReSound in 1984. Perkins was struck by the limitations of acoustic hearing aids.

OVERCOMING OBSTACLES

One of the major challenges in developing the Earlens was ensuring that the contact lens would stay on the eardrum, as the eardrum is naturally designed to remove particles and debris from it.
Rather than adhering to the tympanic membrane, the lens is custom-fit, so that it floats on top of the membrane in a very thin layer of mineral oil for surface tension. In fact, patients are instructed to squirt mineral oil in their ear twice a week, not only to retain surface tension, but to help clean the ear as well.

Miniaturizing the electronics to a size that was commercially acceptable to the patient while meeting requirements to operate a laser via a battery that would fit into a standard-sized hearing aid were two other hurdles.

**UPGRADE**

Earlens is hoping to gain 510(k) clearance from the FDA on its next-generation hearing aid in early 2019. The upgraded hearing aid uses magnetic inductive technology, which Facteau said has significant benefits.

“For our current version, the photodetector has to be exactly in the line of sight of the laser,” Facteau said. “However, we found that in certain patients, when they smile or they chew, their jaw movements cause their ear canals to move. When the ear canals move, the laser moves, which takes it off target and creates slight intermittency. But magnetic induction is impervious to alignment.”

The newer device will be marketed by Earlens’ direct sales force. The technology, like all hearing aids, is not reimbursable in the US through Medicare.

The company has raised $180 million in equity to date, representing four rounds of financing: a $15 million round that closed at the end of 2013, led by individual investors and Medtronic plc; a $37 million round that concluded in June 2014, funded primarily by NEA, Aisling Capital and Lightstone Ventures; a $73 million round that concluded in May 2017, led by Vertex Global Healthcare; and $55 million of the current $87 million round, led by new investor KCK Ltd.

No new capitalization is anticipated within the next year or two, other than the already committed $32 million from current investors. Earlens has two strategic investors, Medtronic PLC and Cochlear Ltd., which have contributed capital only. The company also has a license with Apple Inc. to stream phone calls and music directly from iOS devices, including the iPhone, to its hearing aids.

Facteau said the technology may become even more functional outside of just treating hearing impairment down the road.

“Because the lens sits on the eardrum, this is a great place to collect biometric data for monitoring and alerts, like heart rate and temperature,” he noted. He said a company IPO or acquisition is possible within the next two to three years.

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**WashU Researchers Plan Major Trial Of Noninvasive Radiation Ablation For Ventricular Tachycardia**

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Researchers at the University of Washington in St. Louis are working with the US FDA to design a multicenter trial of their technique for noninvasive cardiac radioablation of ventricular tachycardia using stereotactic body radiation, a technology normally used to treat cancerous tumors that is already widely available.

Stereotactic body radiotherapy is the precise delivery of high doses of radiation to kill specific targets tissue while minimizing damage to the adjacent normal tissue, so it used to control tumors with minimal toxicity, including tumors adjacent to the heart. *(Also see "Global Radiation Therapy Systems Market Expected to Reach $5.6B by 2020" - Medtech Insight, 3 May, 2016.)*

“The beauty of what we’ve invented here for patients is taking an eight-hour procedure and turning it into an 80-minute procedure as an outpatient. [This] is a
major boon for patients and their safety and recovery from this type of procedure," Philip Cuculich, a cardiologist/electrophysiologist at Washington University in St. Louis, told Medtech Insight.

Cuculich also pointed out that the radiation technology needed for this technique is already installed in many centers. "The infrastructure to deliver this treatment is widely available across the globe," he said. "The radiosurgery that we’ve used for this is far more available across the world than cardiac-mapping units are. This really stands to help patients across the globe in terms of receiving potentially life-threatening treatment."

Ventricular tachycardia, a common life-threatening heart rhythm disorder, is often caused by electric reentry within and around heterogeneous myocardial fibrosis. Ventricular tachycardia is usually treated by invasive catheter procedures to map and then ablate the electrical pathways, causing the ventricular tachycardia. Cuculich pointed out that ventricular tachycardia is a leading cause of death across the population, but the techniques available to treat it have many drawbacks.

"We currently have ways to try to rescue people from [ventricular tachycardia], that is, to deliver an electrical shock to jump-start the heart, but that doesn’t improve it or prevent it from happening again," he said. "The process of [ventricular tachycardia]-ablation is potentially dangerous and certainly time-consuming. On average, it takes six to eight hours to do one of those thoroughly. It is associated with a five-percent chance of dying within the first 30 days of procedure. It’s hard on patients. It’s hard on the treatment staff."

Trying to find a less-invasive way to treat these patients led Cuculich to collaborate with Clifford Robinson, the Chief of Service, Stereotactic Body Radiation Therapy and Director of Clinical Trials & Clinical Informatics in the Department of Radiation Oncology at Washington University’s School of Medicine. "We combined my expertise in noninvasive [cardiac] mapping with Cliff’s expertise in noninvasive ablation - typically done on cancer - but in this case done on the abnormal parts of the heart."

Robinson said, "The novel aspect here is using noninvasive imaging to guide the noninvasive, but more importantly, the noninvasive delivery of radiation has historically only been used for the treatment of tumors. It’s never really been used in this way to treat the abnormal part of the heart that has an arrhythmia."

**ENCOURAGING RESULTS SO FAR**

Preclinical studies, beginning about a decade ago, showed that various particle-beam technologies could create histological changes and electrophysiological effects without acute or sub-acute adverse effects and CyberHeart began adapting Accuray’s CyberKnife high-dose radiation device to treat atrial fibrillation, and the company is also sponsoring a small trial of the CyberHeart system to treat ventricular tachycardia. (Also see "CyberHeart Takes Noninvasive Approach To AF Ablation" - Medtech Insight, 19 Jul, 2016.) A 2014 clinical case report from University Hospital In Ostrava, Czech Republic and a 2015 report from Stanford Cancer Institute in California showed that this type of precisely targeted radiation could be used to ablate the aberrant circuits in cardiac tissue that cause ventricular tachycardia.

In 2017, Robinson, Cuculich and colleagues published the results of a five-patient case series in the New England Journal of Medicine showing their ablation technique - combining noninvasive electrocardiographic image mapping and stereotactic body radiation - led to a marked reduction in the burden of ventricular tachycardia in patients whose ventricular tachycardia was otherwise intractable. (Also see "Stereotactic Body Radiation Therapy Could Be Used For Noninvasive Cardiac Ablation, Study Shows" - Medtech Insight, 18 Dec, 2017.)

The procedure also proved to be much faster than cardiac ablation.

"Unlike in a catheter ablation scenario - where they’re anesthetized, put to sleep, and spend some number of days in the hospital - these patients walk in, lay down on the table, get the treatment, and walk out," Robinson said.

Based on that success, Robinson, Cuculich, et al. developed ENCORE VT, an 18-patient, prospective phase I/II trial of electrophysiology-guided noninvasive cardiac radioablation. All the trial subjects were adults who had at least three previous episodes of sustained monomorphic ventricular tachycardia or cardiomyopathy related to monomorphic premature ventricular contractions. All the patients had tried taking at least one antiarrhythmic medication and undergone at least one catheter ablation without success or were contraindicated for catheter ablation.

The researchers used a synthesis of imaging studies and electrophysiological mapping in each patient.

The prespecified baseline evaluations included cardiac computed tomography scan, cardiac magnetic resonance imaging, positron emission tomography/computed tomography scan, 12-lead ECG, and ECG imaging. They targeted radiation on all areas of ventricular scar approximating the ventricular tachycardia "exit site" that harbor related circuits. The linear accelerators used in the trial were Varian Medical Systems Inc.’s TrueBeam and Edge.

The results, published in Circulation in November, show electrophysiology-guided noninvasive cardiac radioablation reduced the median number of ventricular tachycardia episodes from 119 to three in 18 patients over 90 days. All but one of the 18 patients experienced a reduction in their burden of ventricular tachycardia or premature ventricular contractions and the frequency of ventricular tachycardia episodes or premature ventricular contraction burden was reduced by 75% in 89% of patients. The overall survival rate was 89% at six months and 72% at 12 months. Patients’ use of dual antiarrhythmic medications decreased from 59% to 12% and showed improvement in five of nine standard measures of quality-of-life over six months.

No acute toxicity was observed in any of the trial subjects, but 28% experienced delayed pericarditis/effusion and 11.1% had pneumonitis. These were both generally responsive to medical therapy.

In an accompanying editorial, cardiologist Paul Zei and oncologist Raymond Mak from Brigham and Women’s Hospital in Boston write, "There is promise and excitement for this therapeutic modality. The
patient population likely best served initially will be those in whom conventional therapies have failed. Application as a first- or even second-line therapy (after antiarrhythmic drug failure) is premature at this time, but this may change in the future. As we continue to better understand the mechanisms of action of cardiac SBRT and the relationship between the anatomical and electrophysiological markers of arrhythmia substrate, we will likely be able to further refine [stereotactic body radiation] treatment targeting."

Zei and Mak also commend the Washington University researchers for undertaking "the significant effort required to create a new treatment workflow, paradigm, and program that allow effective collaboration between electrophysiological and radiation oncology in an unprecedented way. The importance of a good working partnership cannot be overemphasized, given the complementary skill sets of the two specialties and its impact on delivering effective and safe therapy."

SCALING-UP
ENCORE VT was primarily funded by Washington University and Barnes-Jewish Hospital Foundation competitive grants with some help from a National Institutes of Health grant. The trial did not have industry support.

"[We] do not want to stand in the way of helping patients across the world. We want this to be widely available," Cuculich said. "We want this to be an open platform, so that people can do this procedure and, essentially, democratize the process of [ventricular tachycardia]-ablation."

He said that they hope to work directly with other physicians to develop and refine this technique, but that a "commercial relationship" may help spread this approach faster. "Whatever it's going to take to be able to enable this process is what Cliff and I are looking for," Robinson said.

The multinational trial the researchers are now developing in collaboration with the US FDA will help them learn now to "scale" this technique to more sites while also confirming that it works safely in a larger population.

Robinson said, "There is tremendous potential for variability in how this does get done. So, in some partnerships, we're considering, [we are] coming up with processes where this is done consistently and safely because, within the radiation oncology space, we've seen that variability leads to variable outcomes, and that makes it difficult to interpret data."

Robinson and Cuculich said that they are currently focused on treating the patients with no other options, but eventually this noninvasive technique could be used as a first or second-line therapy for ventricular tachycardia instead of drugs or catheter ablation and/or perhaps to treat other arrhythmias.

"When you're starting with a new technology that had never been used for this purpose, the safest place to do it, and the place that makes the most sense to offer it, was in a 'bailout' or 'salvage' situation," Robinson said. "Once we understand how it can be best used, then we move into the rest of the patient experience. That is, for different kinds of arrhythmias or earlier in the disease progression - this is absolutely a natural progression that we would see."

Arizona Supreme Court Backs Medtronic In Preemption Case

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A new ruling from the Arizona Supreme Court limits the grounds under which plaintiffs can file product liability cases against device manufacturers in state courts.

The case, Conklin v. Medtronic, was brought by a patient who says he was permanently injured by Medtronic PLC's pain pump. Manufacturers are typically protected from suits involving class III devices by the principle of preemption, which limits claims alleging harm caused by devices approved by US FDA. But in this case, Conklin argued that his claim should not be preempted under Arizona law because Medtronic had failed to report adverse events to FDA.

The Ninth Circuit ruled in 2013 in a case called Stengel v. Medtronic that a claim would fall outside the bounds of preemption under Arizona law if the company had failed to report adverse events to FDA. The Supreme Court declined to intervene in the issue in 2015, leaving the Stengel decision standing. (Also see "Preemption Questions Persist: Supreme Court Doesn't Take Bait In Medtronic Case" - Medtech Insight, 2 Jul, 2014.)

However, the three judges reviewing the Conklin case explicitly rejected the Stengel court's reasoning.

"We disagree with Stengel and consequently with the court of appeals' reasoning and conclusion in this case," the judges wrote. "In Stengel, the Ninth Circuit held that the [Medical Device Act] did not expressly or impliedly preempt the plaintiffs' Arizona common law failure-to-warn claim based on Medtronic's alleged failure to submit adverse event reports to the FDA. That holding, however, was
based on the unsupported premises that "Arizona law contemplates a warning to a third party such as the FDA" and that, "[u]nder Arizona law, a warning to a third party satisfies a manufacturer's duty if, given the nature of the warning and the relationship of the third party, there is reasonable assurance that the information will reach those whose safety depends on their having it." Neither premise comports with Arizona law."

The new ruling is only binding in Arizona but is likely to be followed by other state courts, says James Beck, counsel resident in the Philadelphia office of law firm Reed Smith and a frequent blogger about pre-emption issues at Drug & Device Law.

The decision "provides a rationale for rejecting failure to report claims that would apply to pretty much every other state's law," he said, explaining that most states require manufacturers to report potential risks only to specific parties known as "learned intermediaries" – which may include doctors or other professionals who work directly with patients, but typically not regulators like FDA.

"There's no duty to warn the FDA about anything under state law. That's a very simple argument, and the Arizona Supreme Court is the first state high court to consider a failure-to-report claim in the FDA context. So, I think it is a rationale that is persuasive and can be presented in other states," Beck said.

Additionally, the ruling means plaintiffs probably won't succeed with claims based in failure-to-report, he noted. Almost every other kind of claim is already blocked off by preemption, so this ruling further limits patients' lawsuit options, he says.

The perennial question for medtech remains: "How do you get the NHS to adopt at scale?" notes HEE's Anne Blackwood.

As 2018 turns to 2019, the future may be unpredictable for those working in the UK health-care ecosystem, with budgetary pressures on the system higher than ever, greater demand for services, the unknown perils of Brexit and the associated talent shortage, and systemic care staff shortages. That is not to mention a whole new regulatory system for medical technology in the EU, of which, at the time of writing, the UK still remains a part.

Nevertheless, in this fog of uncertainty, there remain bright spots for UK health-care stakeholders, as both industry and the government focus pragmatic approaches to future opportunities. A recent UK conference caught the mood. There is no dimming the appetite for innovation "if it is targeted in the right way," said Anne Blackwood, chief executive of Health Enterprise East (HEE). "It is greater than I've ever known it in the past 15 years," she told Medtech Insight at HEE's Medtech Futures event, hosted by the Wellcome Genome Campus in Cambridge in late October.

"There is no shortage of innovation or ideas, or of those people willing to help get innovations to market. And there is more investment around than there has been – if you've got the right idea and the right people – and can fund it," Blackwood noted. A recent Silicon Valley Bank report touted "record levels of VC investment." So there are lots of positives amid the challenges. And the biggest challenge of all for medtech is not even Brexit, she added, but technology adoption and reimbursement issues. For Blackwood, the perennial questions for medtech remains: "How do you get the NHS to adopt at scale?"

While there are good local examples of new technology being used in the UK NHS, writing a business plan for every hospital is something that an SME simply cannot do. "The pace of adoption in the NHS creates some particular challenges," she said, making the point that the NHS may be "national" by name, but in reality, it's a local health service with largely local and regional adoption systems. However, there are some national programs such as the ITP, under which certain technologies...
that get a tariff can be used by hospitals for free. "There are some levers that the government has introduced, but they do need to be expanded."

For all that, the UK is not alone in this challenge, as similar reimbursement hurdles prevail in other major countries of the EU and beyond. What the UK has as a potential advantage is the availability of data. Here, the NHS would have massive advantages if it could join up this data in sub-populations and thereby facilitate the research that could lead to new treatments being brought forward. "If we get that bit right, we could be real world leaders," said Blackwood. But she is mindful that data ownership is an issue that now ranks alongside reimbursement and regulatory issues as the barriers to overcome in a risk-averse health-care system.

Andrew Laidlaw, an IBM Systems' deep learning specialist, agreed. "Data helps you make sense of the world," he told the Medtech Futures audience. "The first step is to collect, sort and digitize the data, and the second step is to visualize the data and spot patterns," he said. "This technology will change the way we work."

Tech companies have a key role to play in system transformation, but as most of the innovation comes from smaller players, the tech companies will be seeking to spot opportunities to join up with them where appropriate. The challenge for the SME-dominated medtech industry is the length of the sales cycle. "It's cash flow that really kills small companies, and if it takes six to 12 month to make a sale, it can be very hard for them," Blackwood said.

DESIGNING WITH PROCUREMENT AND END USERS IN MIND

For Renfrew Group International's Michael Phillips, good design processes will be an even more valid success factor for medtechs in 2019. Companies, more than ever, must design products with procurement in mind, and be aware of the potential barriers to adoption. Phillips, who is the design development director at the Leicester, UK, product design and technology development company, says clinical entrepreneurs must refine and understand the end-user's needs at every step of design.

"There are so many decision-makers in UK procurement – Trusts, CCGs, et cetera – so you must know who you are selling to and take that into account in the design stages. But it is complicated." Adoption of technologies would be improved if there were some form of universal standard to govern the activity and if best practices were spread by the Academic Health Science Network (AHSNs). Phillips wants NHS England to have some sort of online portal addressing the adoption of innovative technologies. NICE has the MedTech Scan, and there is the ITP scheme addressing funding exemplars for a limited number of technologies. But the sense from Phillips is that these schemes do not go far enough.

In addition, the same frustrations emerge year after year. Government decision-makers have a limited term of office, after which the system could – and usually does – change. What of the effort already made by companies? "It could all be for nothing, and we still have the usual complaints: barriers to adoption, siloes, and in-year budgets held by the wrong people," Phillips says. The Small Business Research Initiative (SBRI) needs to be expanded enormously to make a real impact, he suggests. While it supports and advances good ideas, it needs to be on a bigger scale to make a real difference. Many might simply see it as window dressing. On the other hand, the National Institute for Health Research (NIHR) and i4i (Invention for Innovation) were praised by Phillips.

Speaking to Medtech Insight at Medtech Futures, Phillips suggested that more health economists are needed in government circles and that Treasury-level executives should be empowered to spell out the actual cost and value arguments of each new innovation: it's not a new thought, but it is common-sense approach, he asserts.

Renfrew is currently developing a workstation design for an artificial liver with the Royal Free Hospital and UCL, among other projects. The groups believes there would be system-wide benefits from a more integrated approach to adoption, Phillips said.

In any case, it is essential that health-care regulatory and adoption systems are built to be able to handle advanced technologies such as those of digital health software business xim Ltd. xim and robotics company CMR Surgical Ltd. profiled their advanced technologies at the Medtech Futures meeting to illustrate the changing focus of and needs within the evolving health-care delivery and regulatory frameworks.

"xim has developed a video analytics tool called Life Light, which uses remote photo plethysmography (RPPG) to monitor vital signs. The class Ilib device can be used to triage for urgent care. Company founder Lawrence Pearce explained that the technology offers can help reduce lengths of stay in acute hospitals. The technology has applications as a pre-op assistant in the home or in the clinical space. A CE mark is expected in the first quarter of 2019. xim is looking for early adopters to partner with what Pearce describes as a "transformational technology."

Robotic surgery is hard for many surgeons, hence the currently low rates of use, says CMR Surgical's Mark Slack.

Mark Slack, CMR Surgical's medical director, spotlighted his company's minimal access surgery (MAS) tool Versius at Medtech Futures. "The age of robotic surgery has arrived," Slack told the audience, but added that robotic surgery is hard for many surgeons, leading to low rates of use. As a result, the benefits thus are not coming through to the health economy. There is a need for a robot that can address all surgical disciplines, "a quick modular device," he said, adding that CMR's robot should secure a CE mark in 2019. (Also see "CMR Surgical Launches Robotic System To Rival Intuitive's Da Vinci" - Medtech Insight, 5 Sep, 2018.)

A CHALLENGE FOR 2019

Cambridge in the UK has traditionally been more famous for biotech, but in-
novative medtech, artificial intelligence (AI), data and digital themes are driving much current local research, making the medtech sector more prominent. Nonetheless, HEE’s Blackwood says age-old problems need to be properly addressed.

One of the biggest current challenges, she said, is NHS resource constraints, which she sees as an implementation problem. "We don’t spend enough money on adoption and implementation," she said. New technology is one thing, but what the providers don’t have is time – i.e. the time to change what they are currently doing to adopt new, improved processes. "This is the biggest barrier: the NHS is so "hammered" that it doesn’t have the bandwidth to stop and change; they are all too busy on the ‘day job.’"

Blackwood says there must be a time ahead when the NHS is able to create, promote and manage risk appropriately to support adoption of innovation. The alternative is leaving "great technologies" to collect dust on the shelf, unused, she said. But Blackwood is optimistic about the UK’s renewed focus on driving value. "It’s inevitable that we’ll reach that tipping point on the adoption of technology in the NHS at greater pace and scale. And we’re not that far away from that."

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**Health Enterprise East – Part Of The UK Innovation Ecosystem**

HEE is a partner to the Eastern Academic Health Science Network (AHSN) – one of 15 AHSNs in England – and works with the NHS and industry to develop innovations. HEE was set up in 2004 with NHS funding, and so far has supported 25 NHS organizations, created six new companies, evaluated 2,000 ideas, brought 125 technologies to market and leveraged £15m ($19m) in public-health private-sector investment value creation. Its Medtech Accelerator showcase is a £2m public sector joint venture that provides proof of concept funding for NHS staff who have ideas for new products or services. A year ago, HEE raised £9m to set up Medovate, a company supported by private-sector funding that works with industry partners on a remit to supply specialist management resources and finance to support innovation development through to clinical trials and regulatory approval.
Breakthrough Pathway Final Guidance Eases Sponsor-Regulator Interaction Requirements

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Two years after Congress passed the 21st Century Cures Act, US FDA has finalized a guidance that lays out a pathway that fast-tracks certain high-priority medical devices by easing interactions with regulators. And in one major part of the guidance, the agency outlines conditions for “sprint” discussions to ensure sponsors get quick responses to important development questions.

As part of the 21st Century Cures Act, lawmakers required FDA to develop a new pathway called the Breakthrough Devices Program. Similar to the Expedited Access Pathway (EAP) already in operation that the new pathway supersedes, the Breakthrough program is intended to help speed the development of innovative devices and device-led combination products that are considered to be more effective, or diagnose life-threatening or irreversibly debilitating diseases or conditions. FDA says devices already in the EAP are automatically grandfathered into the Breakthrough program.

A little over a year ago FDA released a draft version of the guidance that outlined the program (and superseded the agency’s Priority Review Program). In the draft, the agency allowed 510(k) products as part of the program and removed certain requirements such as insisting sponsors have a long-term “data-development plan” drafted before being allowed in the program. While elements such as having a data-development plan are still an option in the final guidance, they are not requirements like they were in the EAP program. (Also see “Breakthrough Blueprint: US FDA Draft Guideline Outlines Revised Expedited Development Program” - Medtech Insight, 24 Oct, 2017.)

In an agency statement announcing the final guidance, FDA Commissioner Scott Gottlieb noted that the objective of the program is to provide a more agile pathway for developers of breakthrough devices, which allows them to get better feedback from the agency on what kind of information is required for a speedy review.

“We know from experience that more frequent interactions with device developers during product development can result in identifying more efficient ways of evaluating these novel devices’ benefits and risks, and facilitate a timelier pre-market review, which is especially important since timely patient access is critical with these types of devices,” said Gottlieb.

“To achieve these goals, the final guidance outlines several program options to efficiently address device development topics as they arise to best facilitate efficient development, such as sprint discussions – meetings between the FDA and sponsors who need timely resolution of focused issues, such as testing protocols – requests for feedback on a data development plan, and requests for clinical protocol agreement,” he added. “These options improve the efficiency of the FDA’s review resources and are designed to facilitate entry of state-of-the-art medical technologies to the market without compromising the standards for marketing authorization.”

According to FDA spokeswoman Alison Hunt, the main comments the agency got in response to the draft guidance that resulted in updates to the language included requests for clarity on the eligibility of combination products, policies for review of marketing submissions for multiple breakthrough devices that addressed the same unmet clinical need, and application of priority review. The agency also heard back from stakeholders to clarify how the designation process is related to the review of subsequent regulatory submissions, such as Q-submissions and marketing submissions.

In response, Hunt said FDA updated the guidance by clarifying that device-led combination products are eligible for inclusion in the Breakthrough Devices Program and provided more details on how the device center plans to work with other product centers during the review of regulatory submissions for device-led combination products designated as breakthrough. The agency also gave more detail and examples to illustrate its policy for review of subsequent marketing submissions when multiple devices have been granted breakthrough designation for the same unmet clinical need.

Hunt also clarified that devices that have been designated as breakthrough will receive prioritized review for their subsequent regulatory submissions, including Q-submissions, Investigational Device Exemptions and marketing submissions.

“We revised the order of guidance sections entitled ‘Designation Request’ and ‘Program Features’ to better align with the sequence of events that a sponsor would follow when requesting inclusion in the program and subsequently utilizing its features,” she added.

As noted earlier, the Breakthrough program supersedes the EAP, which was used to expedite certain devices until the final Breakthrough program guidance was published. The agency has been transitioning away from that program. To date, Hunt says FDA accepted 25 devices into the EAP.

“As of Dec. 1, 2018, an additional 85 devices were granted Breakthrough Device designation,” she said. “Therefore, as of Dec. 1, 2018, there are 110 devices included in the Breakthrough Devices
FDA Marches Forward With 'STeP' Program To Aid Development Of Significantly Safer Medtech Products

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U S FDA will use some of the principles and features of its successful Breakthrough Devices Program for a planned Safer Technology Program (STeP) that’s designed to hasten the market entry of devices that are determined to be safer than current alternatives.

The program was first described by FDA in April as an outcome of its so-called Medical Device Safety Action Plan. (Also see “New Safety Framework Mixes Current Efforts, New Investments At US FDA” – Medtech Insight, 17 Apr, 2018.)

“The best technological advances should lead to more lives saved and few adverse events,” said FDA Commissioner Scott Gottlieb and device chief Jeff Shuren, in touting the STeP program.

“The best technological advances should lead to more lives saved, fewer adverse events, and improved quality of life,” FDA Commissioner Scott Gottlieb and device center Director Jeff Shuren said in a joint Dec. 18 statement. The STeP program, they added, is at the core of FDA’s vision to support safety advances in medtech products to help improve patients’ quality of life and advance the agency’s public health mission. Gottlieb emphasized his intent in mid-November to push forward a series of initiatives to ensure that only the safest of devices are approved or cleared by FDA for market, and the STeP program is clearly part of that initiative. (Also see “FDA Looks To Lead World In Post-Market Device Surveillance With Safety Plan, Investments” – Medtech Insight, 20 Nov, 2018.)

FDA’s Breakthrough Devices Program is an accelerated development pathway for products that the agency finds could provide a more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions, addressing an unmet need. Meanwhile, STeP would be reserved for devices that meet almost all of the criteria to be part of the Breakthrough program – except that they are designated for non-life-threatening diseases or conditions – but through innovative designs have the potential to be significantly safer than currently available alternative treatments or diagnostics.

EXAMPLES OF ORTHOPEDIC, MEDICAL IMAGING PRODUCTS THAT WOULD FIT STEP

Gottlieb and Shuren provided two examples of devices that could be considered for STeP. One example offered is of an orthopedic device that treats a condition that is neither life-threatening nor irreversibly debilitating (and would therefore not meet the Breakthrough pathway criteria) but could qualify for STeP if it included an innovative safety mechanism that was intended to reduce post-surgical complications.

A second example is of a medical imaging device that also does not meet breakthrough device criteria, but significantly reduces radiation exposure in comparison to similar imaging devices.

While the two FDA programs fostering breakthrough devices would follow different pathways, “they could have similar impacts in spurring the development of, and giving patients more timely access to, important medical devices,” Gottlieb and Shuren said. “If the same programmatic benefits that encourage manufacturers to create devices to treat or diagnose a life-threatening disease can be applied to bring innovation to medical device safety for less serious conditions, the potential public safety impact could be tremendous.”

ACTION ON STEP WILL BE TAKEN IN FIRST HALF OF 2019

Gottlieb and Shuren said their goal is to provide the STeP program as an option for device manufacturers in the near future. “In the coming months, you’ll hear more from us about our thoughts on STeP and how it could be used to bring important advances to device safety and innovation to improve public health,” they said.

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MORE TARGETED APPROACHES ARE TIME-CONSUMING
Thompson believes FDA could address problematic predicates in a more targeted manner via special controls on the affected devices.

In its recent reform proposals, FDA emphasizes the importance of special controls, but notes that the process for instituting special controls on an existing device category is “lengthy and inefficient.”

In addition to special controls, the other approach that is also more targeted that discouraging or prohibiting predicates based on age is upclassifying a device type into class III and requiring PMAs. That’s the approach FDA says it has taken to eliminate almost 1,500 devices as legal predicates since 2012. But the reclassification process, FDA notes, is also “time- and resource-intensive, and not a good fit for swift action in response to safety concerns.”

FDAs’s looking for a pathway to streamline the processes of imposing special controls and upclassifying devices to address safety concerns. This could require Congressional help, the agency said.

510(k) rescission is another regulatory tool that FDA has tried to use in the past. But rescission has run up against legal barriers and it wasn’t mentioned in the latest reform proposal.

Another more targeted regulatory tool that the agency has tried to use in the past, but which it did not mention in its latest proposals, is rescinding a 510(k), which would effectively take a product off the market and remove it as a predicate at once. But FDA has run up against legal barriers in applying 510(k) rescission.

In 2011, the agency rescinded ReGen Biologics Inc.’ Menaflex collagen scaffold device for repairing and reinforcing knee meniscal tissue. But in 2014, a federal appeals court ruled that the agency should have used the more time-consuming reclassification process to address concerns with the device clearance. (Also see “Appeals Court Checks FDA On Its 510(k) Rescission Authority” - Medtech Insight, 29 Sep, 2014.) As a result, FDA would likely need Congress to pass legislation to clarify its authority if it wanted to put rescission on the table.

“FDA is not allowed to make a mistake, basically, because it is really hard to rescind a 510(k),” said former ODE Director Christy Foreman. “I think exploring rescission authority would be a better solution for addressing predicates of concern, or, alternatively, identify ways to more efficiently develop special controls or performance standards to address concerns with a category of devices. Establishing an “arbitrary line in the sand” for all 510(k) devices “can throw the baby out with the bath water,” Foreman noted.

Defining FDA’s authority to rescind a 510(k) and plans to issue guidance on when it’s appropriate to retire a 510(k) predicate, were both proposed by FDA the last time significant 510(k) reforms were on the table, between 2010 and 2012, when Foreman was at the helm of ODE under current CDRH Director Jeff Shuren (Foreman left the device center in 2014). But neither of those proposals, nor several other substantial policy reforms raised at the time, were ultimately adopted. (Also see “CDRH Drops Seven Divisive 510(k) Proposals; Congress Picks Some Up” - Medtech Insight, 27 Feb, 2012.)

QUESTIONING FDA’S AUTHORITY
Exactly what FDA can do to update the 510(k) program without authorization from Congress is up for debate. The agency seems to acknowledge that some of its plans will likely require legislation, while other parts of its proposal may not.

Some in the medtech legal community, however, argue that the whole plan would violate federal law under FDA’s current authorities.

“A regulatory agency is not imbued with the power to create law outside of the parameters set by Congress,” attorney Thompson write in response to the recent proposals. “An agency that proposes a pathway that contradicts or exceeds congressional directive expressed in statute violates the law.”

Thompson says that FDA’s proposals would rewrite the 1976 legislation that created the 510(k) process. He acknowledged that FDA suggested some of its proposals might require congressional intervention, but Thompson said that wasn’t enough.

“FDA’s statement seems intentionally coy so that FDA can’t be held accountable if they proceed with anything and everything included in this statement without seeking congressional authorization,” he wrote.

Attorney Mark DuVal, president and CEO of DuVal & Associates, agreed, arguing that the plan “is unquestionably illegal.”

King & Spalding’s Hoang and Tseng, had a more measured response. They agree that congressional intervention will likely be necessary before FDA can “sunset” older devices. Specifically, language would need to be added to the regulations defining a predicate device because the current rules do not include anything about predicate age, they said.

But Hoang and Tseng believe that, even without Congress, FDA could launch the proposed online list of devices relying on older predicates. The agency could also move ahead with a voluntary pilot program that offered faster review times, such as the recently implemented Quik-510(k) pilot, which promises faster reviews for firms that make electronic 510(k) submissions using a standardized template, they said. (Also see “Quik’ Review Program Builds On US FDA eSubmission Efforts” - Medtech Insight, 5 Sep, 2018.)

“It may be that in the future, rather than providing blanks for the applicants to fill, FDA could incentivize reliance on newer predicates or state-of-the art technology by listing specific performance criteria for applicants to select as they fill out the electronic form in order to qualify for the pilot program’s benefits when requesting clearance for their devices,” they said.

But Thompson argued that listing products relying on older predicates would violate US Department of Health & Human Services rules around the release of information, he says. The HHS regs require that information that is released is accurate and “ful-
fills an authorized purpose. “A public release of merely a list of those products using older predicates does not accurately convey the safety and effectiveness profile of the products on the list,” Thompson says.

DuVal questioned whether FDA was unnecessarily intervening in the market by listing products in a manner that shines a negative light so that companies feel an incentive to find newer predicates.

Companies that want to get ahead of the issue may want to submit a “catch-up” 510(k) for devices that are more than 10 years old, King & Spalding’s Hoang and Tseng recommend.

“FDA seems to be substituting its judgement for the medical marketplace,” DuVal said. “Is that FDA’s job?”

510(k)s, he said, are meant to be the “workhorse” of medical device regulations, drawing on familiar ground while taking into account new obstacles. The program, he argued, is flexible enough to handle new technology.

GETTING AHEAD OF THE REFORMS?

As of now, FDA has just made some general proposals. FDA’s next step will likely be opening a formal notice-and-comment period on some of the proposed changes, Hoang and Tseng say. Commissioner Scott Gottlieb has said he is briefing members of Congress on some of the proposals, while the agency collects input from industry and others.

Device center Director Jeffrey Shuren has promised to seek public comment specifically on the proposal to set 10 years as a standard for older predicates. Additionally, the agency is reviewing comments that came in on its draft guidance to establish the alternative 510(k) pathway (now called the “Safety and Performance Based Pathway”) allowing certain products to gain a substantial equivalence finding using objective safety and performance criteria, rather than device-to-device comparisons. Industry was underwhelmed by the draft, but FDA says it plans to finalize the guidance early next year. (Also see “FDA’s Alternative 510(k) Proposal Falls Flat With Industry” - Medtech Insight, 20 Jul, 2018.)

Meanwhile, companies that want to get ahead of the issue may want to submit a “catch-up” 510(k) for devices that are more than 10 years old, Tseng and Hoang recommended. The submission could include any changes made to a device in the intervening years, which might help preserve the ability to use the device as a predicate in the future.

If FDA is ultimately able to move forward with its proposals, it’s unclear how it will change life for device-makers. AdvaMed CEO Scott Whitaker told investors on a recent conference call sponsored by Wells Fargo that he doesn’t expect meaningful changes to the time and cost of bringing new devices to the market.

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director for Lachman Consultant Services and a former US FDA investigations branch director, told Medtech Insight that the database could give firms a leg up in both the pre- and post-market arenas.

“I think, from a manufacturer’s point of view, it is a good data repository for them for a few reasons,” said Chase, who joined Lachman in 2016 after spending 16 years at FDA, where she was also an investigator, medical device specialist and supervisor investigator.

“For one, firms can make sure that information they have on which they’re basing things like 510(k)s, for instance, is valid. Because when you’re going to do a 510(k), you want to understand what your predicate device is going to be, and you want to understand what problems there might be with that predicate device,” she said.

“And from a post-market point of view, it would be expected that manufacturers would be keeping their finger on the pulse of their competitors that have those predicates, or same or similar devices coming onto the market,” Chase added.

“So, collectively, if you make infusion pumps, then you really need to have your finger on the pulse of what’s going on in the infusion pump market and what some of those issues are.”

Chris Harvey, director of recall solutions with consulting firm Stericycle, agreed with Chase’s assessment.

“If a manufacturer is developing a new product or has a similar product in the market already, they’ll want to know what some of the issues are that are occurring with those devices, and the recalls that have occurred,” he said in an interview.

The database “does give firms a mechanism to be able to proactively look at, say, what are the other catheter recalls, and what the reasons were for those recalls,” Harvey said. “It doesn’t necessarily give you the full root cause analysis, but it does give you a bit of background on the issues that are occurring.”

A BROADER VIEW OF DATA

While companies can use publicly available recall and adverse-event data from

"From a marketing standpoint, the database gives you some intel into what’s happening with competitors. That’s very valuable," consultant Chris Harvey says.
FDA to help them make decisions about the products they make, information in the IMDD gives manufacturers a more global view of what’s going on with a particular device.

“For quality and regulatory folks, a lot of times they’re just looking at recalls published in the FDA Enforcement Report, looking for trends, looking for what’s happening with products that are similar to what they make,” Harvey said.

“But what this new database does is provide added historical visibility, not only for the US, but for some of the other regions around the globe on what’s happening. And they can use that to make their product safer,” he said.

Consultant Chase says “the problem with FDA’s data is that it’s limited to the FDA. So, the most obvious plus to manufacturers is that the [IMDD] draws in post-market information from other countries of interest.”

She pointed out that some device firms “try to draw a line in the sand” by telling FDA that OUS post-market data on same or similar products is irrelevant and doesn’t warrant collection.

“But it’s not irrelevant,” Chase said. “FDA has said that manufacturers have a responsibility to understand what’s going on in the market with same or similar devices, and that market isn’t defined only as the United States.” The new international database helps firms fulfill that agency expectation.

And device-makers can gain insight into competitors by using IMDD data – an advantage for companies that might not otherwise be able to find that type of information on their own.

“To be able to look at data on competitors is a huge plus, because right now, extracting that type of information from the EMA [European Medicines Agency], or the UK’s MHRA [Medicines and Healthcare products Regulatory Agency], or Health Canada – it is extremely challenging. So, having at least some of that data in one place is very nice,” Chase said.

Again, consultant Harvey agreed. “From a marketing standpoint, the database gives you some intel into what’s happening with competitors. That’s very valuable.”

He also singled out Europe as a region that is difficult to extract medical device post-market data from. Information from only three European countries – Switzerland, Spain and the Netherlands – is currently found in the IMDD, which is hardly representative of the EU as a whole.

“The thing is, within Europe there are different competent authorities and there are different nuances from country to country. So you’re not getting the full picture by only getting data from a few countries within the EU,” Harvey said. “That’s definitely something that’s a good call-out and important for a user of this database to understand: that there’s still a number of recalls that are not included in [the IMDD]. It’s just a snapshot of some regions.”

Harvey, whose firm publishes a quarterly recalls index for a variety of commodities, hopes the new database will spur other countries and regions to add to it.

“We often find it difficult at Stericycle to get data from certain countries on what’s being recalled, especially in the pharmaceutical and device industries,” he said.

**IMDD: First Impressions**

**Ricki Chase:** “Manufacturers will be able to work within the system and understand what they’re looking at. They understand the interrelationships between, say, somebody who quote, ‘owns’ a product, and somebody who might be having somebody else manufacture it for them – that type of thing, and all the different nuances that go along with product ownership. So, I think they’ll be able to ferret that out. And the database appears to be very comprehensive.

Obviously, I have no way to validate the data, but it appears to be very comprehensive, which is good.

“I found the database to be slightly annoying, though, in that it wouldn’t let me sort my findings by date. I specifically looked for a recall I knew was old but ongoing, and it wouldn’t let me sort those records by date. And a lot of times it takes three or four clicks to get to the data you’re looking for. And you really have to pay attention to the dates. Is this something that happened in 1991 and the product is still not on the market? Or is it something else?”

**Chris Harvey:** “I found it very easy to access the data through a zip file. The data is very comprehensive. It’s broken down into a few different spreadsheets.

There’s a need for the viewer to sort through the data quite a bit, but it does give visibility to historical recalls and the manufacturers. But the user would still have to really roll that data up.

“The data is very granular, so having some type of rollup or filter system would assist a layperson with being able to narrow down the data they’re looking for. But someone who is a little more experienced with recalls, I definitely believe there’s some value with this database. It’s a good start. We [at Stericycle] are going to definitely review this data and see what opportunities there are for us to use it.”
"Consumers are not stupid. If they're so interested in device failures that they're going to look at this data, then they're going to look at this data in a way that they can hopefully draw some conclusions," she said. "If they care enough to [use the IMDD], then they're doing it for a reason. Because your average person isn't thinking, 'Oh, I'm just really curious about post-market data on medical devices.'"

Because the database offers a greater visibility of device troubles, highly interested consumers familiar with industry will likely hold manufacturers' feet to the fire even more when they make products that malfunction.

"And if you couple that with FDA's initiatives to get patients more involved in medical devices and medical device development, and to use real-world data in making decisions about benefit-risk analysis of medical devices, this database gives more information that can be brought in and considered," Chase said.

Added Harvey: "The database gives visibility to what issues are occurring and why. For example, in our latest recall index we noted that software was the top recall cause for the 10th quarter in a row. Someone looking at this database can probably start to identify that problems with software is a common issue occurring with device manufacturers."

"So, I can see where there could be a little more pressure on device manufacturers to understand what's causing those problems," he continued. "Are they rushing to market? Are they not investigating as much as they need to? This kind of data could bring some of that up to industry."

**USEFUL FOR MANY, CONFUSING FOR SOME**
The new database also gives patients the flexibility to research the safety history of any device that a physician might use on them.

"Let's say you're going to have your knee or hip replaced," Chase said. "I always tell people, don't agree to do that until you ask the physician – and be very specific – which device they intend to use, clear down to the manufacturer, make and model. And then go do your homework."

The IMDD "allows patients to have more of a voice and to do that type of homework, so they can come back to the doctor and say, 'You know, so-and-so company has had a lot of recalls and I'm a little concerned about that,'” she said.

"Unfortunately, many doctors – many doctors – are completely oblivious. And if you say, 'This company has had a lot of recalls,' the doctor will probably say, 'Oh, it's fine,' because some representative got that doctor to sell that company's artificial knee," Chase said. "But the IMDD database does allow the consumer to have that discussion and have a voice about potential concerns, and I think there's value in that."

But while she believes the IMDD can "benefit a savvy consumer," Chase said she's worried about the ability of laypeople to digest the data, which can be confusing for those outside industry.

In fact, ICIJ admits on an FAQ page: "This is not easy data to understand."

"You're going to see problems pop up when less-savvy consumers fish around for XYZ device, and they look at the database information, and they don't know what it means," Chase said.

"There are a lot of nuances with this data, and if consumers don't really know what they're looking at, they can become easily confused," Chase said. "Either they'll draw completely wrong conclusions that make the picture look worse than it is, or they won't draw the proper conclusions, which would really tell them how bad things are."

"It's really good in a lot of ways, but I think the database has some room for improvement in the way people could look for and understand the data from more of a novice point of view."

For example, Chase suggested the addition of a so-called “alias” function to use when searching for a particular firm.

"I've seen some databases that use that alias function," she said. "What happens is, if somebody types in, say, 'Fresenius,' then a menu pops down and says, 'All of these companies are related to Fresenius.' That way the researcher can understand that these other companies are related to Fresenius in a corporate-wide relationship. That would tell a lot about the company as a whole, and not just about a particular product."

Chase said database users could get a better picture if the IMDD would link companies that are under a corporate umbrella and interrelate their data.

"Look, the database is good, but it's like any other new tool: as it grows, they'll get feedback, and it will get better and better," she said.

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