Medtech Insight
Issue 63
medtech.pharmamedtechbi.com
Pharma Intelligence Informa
October 2, 2017

HOLDING OUT FOR HOME HEMODIALYSIS:
Still-Modest Market Promises Bigger Growth

JENNY BLAIR jennyblairmd@gmail.com

According to the US Renal Data System's 2015 report, 468,000 patients in the country underwent dialysis in 2013. Globally **Fresenius Medical Care AG & Co. KGAA** , the largest dialysis service provider, estimates that there are currently three million patients with kidney failure that regularly undergo dialysis. And their numbers are expected to rise, driven in part by the increase of chronic diseases such as obesity and diabetes.

The cost of treating these patients is also substantial. In 2013, the Centers for Medicare and Medicaid Services (CMS) spent $30.9bn on these patients, accounting for 7.1% of total expenditures. Many believe that alternative approaches, such as HHD, could help rein in some of the huge cost burden of treating patients at centers.

"A lot of people who are pretty smart in the clinical community and the business sector are expecting that HHD, which is now basically a niche, is poised for a rapid expansion," said John Milad, CEO of **Quanta Dialysis Technologies Ltd.**, a UK-based startup that has developed a personal hemodialysis system.

Bad Homburg, Germany-based dialysis giant Fresenius ranks among them. It announced on Aug. 7 that it struck a $2bn deal to acquire US-based home dialysis equipment maker **NxStage Medical Inc.** whose FDA-cleared *Solo system* allows patients to perform their own HHD without a care partner *(Also see "Fresenius Homes In On NxStage" - Medtech Insight, 7 Aug, 2017.) (Also see "Number To Know…30" - Medtech Insight, 8 Aug, 2017.)*. The deal is subject to close by 2018, pending antitrust review.

The benefits of home hemodialysis is expected to drive the market for enabling technologies

Shutterstock sciencepics

"This acquisition is yet another writing on the wall that the current way of delivering dialysis is not sustainable in the long run — the traditional centers being very labor-intensive, capital cost-intensive, and difficult to scale to treat the rapidly growing population," said Ruey Feng Peh, CEO of the Singaporean startup **Advent Access**, whose first product is a device to ease vascular access for dialysis patients.

"It's at a point where major stakeholders must pay attention to these problems and provide a better solution," Peh added.

But not everyone is so bullish.

Last June, **Baxter International Inc.**, Fresenius' chief rival in the US dialysis equipment market, cancelled its hotly anticipated HHD program, dropping the CE-marked *VIVIA* dialyzer from further development.

CONTINUED ON PAGE 20

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

SAVE THE DATE

November 8-9, 2017

Join us for MDMA's 20th Coverage, Reimbursement and Health Policy Conference to be held in Baltimore on November 8-9, 2017.

Leading experts and policy makers will share the latest strategies on how to secure fair and adequate reimbursement for your products, and what ongoing reforms with public and private payors will mean for your growth.

Top Sessions Include

- Interactive Case Studies Analysis
- CMS Policy Makers Update
- Demonstrating Value to Providers
- Developing the Right Clinical Data
- Navigating the CPT and RUC
- Latest International Reimbursement Trends
- And many more

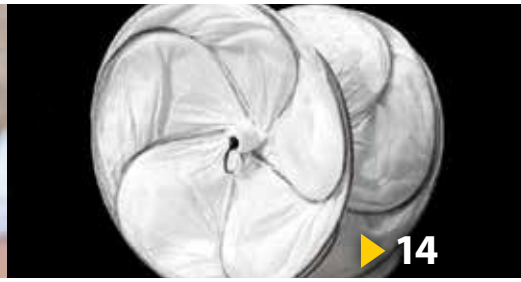
Coverage, Reimbursement and Health Policy Conference

The Westin – BWI

MDMA Members: $695 | Non-Members: $895

Register today at medicaldevices.org

MDMA
MEDICAL DEVICE MANUFACTURERS ASSOCIATION



explore more:

exclusive online content

US FDA, tech and medtech
http://bit.ly/2xxCm6G
Tech luminaries Apple and Fitbit will join the likes of J&J and Roche in a new FDA pilot program to map out a "pre-certification" program for health software.

More questions on EU standards
http://bit.ly/2yGS7pS
EU policymakers are looking to prioritize what standards should be harmonized to the new Medical Device and IVD Regulations, but the process could leave some companies in a fog of uncertainty.

New CEO for "smart" inhaler-maker
http://bit.ly/2k3Heef
Newly appointed CEO Arik Anderson of Adherium is planning to put the maker of smart inhalers on the fast track to growth. Find out what his strategy is.

Peripal aids PD growth
http://bit.ly/2fQLrNY
Swiss start-up Peripal believes it can contribute to the growth of the peritoneal dialysis market with its coupling device designed to reduce procedure complications. Read our Start-Up Spotlight on Peripal.

Device Week
http://bit.ly/2v0IJtS
US reforms to FDA's facility inspections process are the focus of the most recent episode of *Medtech Insight*'s weekly podcast – and keep an eye out for our upcoming discussion on social media in medtech and other topics.

medtech.pharmamedtechbi.com

inside:

Medtech insight

DAVID FILMORE @MEDTECHDAVID
david.filmore@informa.com
TINA TAN @MEDTECHTINATAN
tina.tan@informa.com
SHAWN M. SCHMITT @MEDTECHSHAWN
shawn.schmitt@informa.com
REED MILLER @MEDTECHREED
reed.miller@informa.com
AMANDA MAXWELL @MEDTECHAMANDA
amanda.maxwell@informa.com
MARION WEBB @MEDTECHMARION
marion.webb@informa.com
SUE DARCEY @MEDTECH_INSIGHT
sue.darcey@informa.com
FERDOUS AL-FARUQUE @MEDTECH_DANNY
danny.al-faruque@informausa.com
ELIZABETH ORR @ELIZABETHJORR
elizabeth.orr@informa.com
CATHERINE LONGWORTH @MEDTECHCATE
catherine.longworth@informa.com
ASHLEY YEO @ASHLEYPYEO
ashley.yeo@informa.com
MAUREEN KENNY @SCRIPREGMAUREEN
maureen.kenny@informa.com
NEENA BRIZMOHUN @SCRIPREGNEENA
neena.brizmohun@informa.com
VIBHA SHARMA @SCRIPREGVIBHA
vibha.sharma@informa.com
JANET HANIAK SENIOR DESIGNER
GAYLE REMBOLD FURBERT DESIGN SUPERVISOR
RICHARD FAINT HEAD OF MEDTECH
richard.faint@informa.com
PHIL JARVIS MANAGING DIRECTOR

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

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

▶ join the conversation

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

@Medtech_Insight

EU ROADMAP: Finalized Plan For Implementing New Regs Coming Next Month?

AMANDA MAXWELL amanda.maxwell@informa.com

The long-awaited roadmap to the implementation of the Medical Devices and IVD Regulations, being drafted by the European Commission in conjunction with the Competent Authorities for Medical Devices (CAMD) group, should be ready within the next few weeks, sources suggest.

The hope is that the final roadmap will be available by mid-October, ahead of a stakeholder day on the new regulations that will be jointly organized by the Commission and CAMD on October 18. Other medtech sector stakeholders, such as notified bodies and industry, will also be invited.

This event had not been widely publicized, but it is an event that had been called for by former head of regulations at the Medtech Europe industry association, John Brennan, as providing "a critical opportunity for the regulatory authorities, notified bodies and industry to identify and prioritize shared concerns that need urgent attention." *(Also see "Q&A: With New EU Regs Taking Effect, What Can Industry Do To Be Proactive?" - Medtech Insight, 28 Apr, 2017.)*

Niall MacAleenan, a member of the executive group of the CAMD and medical device lead at the Irish Health Products Regulatory Authority (HPRA), told *Medtech Insight* the roadmap is intended be a practical guide for regulatory authorities and the Commission to work together towards implementation.

MacAleenan, who made emphasized that he was giving his own opinions rather than an official CAMD view, added that the mapping process will hopefully increase clarity, avoid duplication and identify challenges to address.

It will also be fluid: The roadmap could change over time with changing priorities when new challenges are identified, he said.

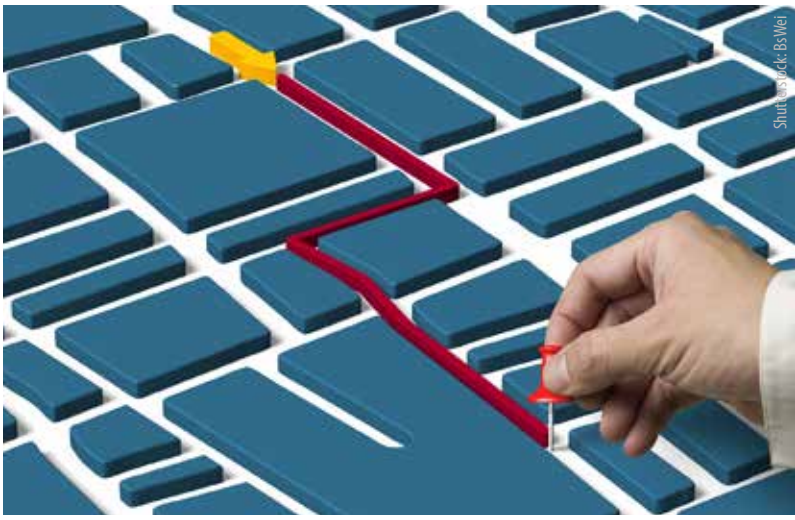
The work itself outlined in the roadmap will by and large be taken forward by the different working groups, and will involve industry, *Medtech Insight* understands. "The roadmap is useful," MacAleenan noted, "but much more important is ensuring participation and resource from all involved to achieve the implementation work."

THE SEVEN PRIORITY CLUSTERS

The draft roadmap that was shared in March features seven different proposed implementation priority clusters, each including multiple work items. It is not expected that the basic structure has not changed since then.

The seven road map priority clusters decided in the latter part of last year are:

1. Notified bodies, including how to get them redesignated, as well as addressing capacity issues;
2. Clinical issues, including drafting common specifications and more clarity on clinical evaluations and equivalence issues;
3. Issues surrounding classification and scope, including reclassifying some devices from the legacy device directives to the Medical Device Regulation, as well as new rules for software and aesthetic devices;
4. Registration, including Unique Device Identification, looking at how the supply chain deals with the single registration number, and implant cards;
5. Market surveillance, including looking how to coordinate liability;
6. Vigilance, including looking at periodic safety update reports, how the Eudamed medical device database can be integrated, and how data can be used for improving patient safety and oversight of the system; and
7. IVD-specific issues, including companion diagnostics.



Shutterstock: BsWei

WHY IS ROADMAP IMPORTANT TO INDUSTRY?

Industry is hoping that the publication of the roadmap will also help confirm timeframes for compliance, as there are many derogations, or exceptions, in both the device and IVD texts, and these are creating some difficulty in interpretation.

MedTech Europe has been working on its own best-practice guides for its industry members addressing each of the main areas of implementation. The trade association is keen to access the final roadmap to see if there are any additional items that need addressed or that need to be re-prioritized.

WHAT IT DOES NOT DO

One matter the roadmap will not address is setting out how notified body designations will be managed. That will be a specific operational aspect that will be discussed by the relevant working groups and by implementing measures from the EU Commission, MacAleenan said. Draft implementing measures have already been made public. *(Also see "Notified Bodies Apply For EU MDR/IVDR Designations*

Despite Document Shortfall" - Medtech Insight, 14 Sep, 2017.)

Nor will the roadmap will set out details regarding the delegated and implementing acts for the new regulations.

MacAleenan said the roadmap "may point to the potential for working groups to contribute to the development of implementing measures in different areas. However, the requirement for these, the order in which they will be produced and corresponding timelines will be addressed separately by the EU Commission.

IVD ISSUES

There have been questions about how issues related to the implementation of the IVD Regulation are being managed within the roadmap. When it comes to IVDs, MacAleenan explained that the roadmap has an IVD-specific workstream to address issues that are only relevant to the IVD Regulation. The other IVD aspects, he said, are best captured in the specific technical cluster to which they are relevant or in circumstances when they are general/horizontal aspects.

Published online 09/22/17

What Is CAMD And What Is Its Role?

CAMD is an umbrella group under which the national competent authorities in the EU work to enhance collaboration, improve market surveillance, and deliver better communication

It set up a task force in October 2016 to focus on implementation of the Regulations and is playing a pivotal part in work on the European Commission's medical device roadmap. The roadmap should clearly lay out CAMD's role in terms of its implementation objectives.

The group was one of the organizers, along with the European Commission, of the stakeholder meeting on the implementation of the regulations, which took part in Brussels on March 9 and where proposals to tackle implementation in the context of seven different clusters were reviewed.

COMPLIANCE CORNER:

Abbott Quality VP Wants You To Talk About These 5 Things At Management Reviews

SHAWN M. SCHMITT shawn.schmitt@informa.com

Too often, medical device manufacturers are more concerned about being compliant with US FDA's rules for conducting management reviews than learning anything of value from the meetings.

"When management reviews become paper exercises to be compliant, that's a problem," said Monica Wilkins, divisional VP of medical, quality and strategic support for device-maker Abbott Laboratories.

"Firms that do that will go through the motions and have some level of discussion, but they do it more to say, 'I'm agreeing. My quality system is effective and I've moved on.' That's when you're looking at compliance versus really getting engaged and looking at quality system improvement," she said.

At Abbott, Wilkins says the firm wants to make sure that everyone participating in management reviews is involved and alert. "I expect engagement and I don't want attendees to sift through the material presented and just say, 'Check. Everything's good. Let's move on.'"

Wilkins made her comments at a Case for Quality Metrics Workshop in Cincinnati hosted by the Medical Device Innovation Consortium (MDIC) and Xavier University. (In a separate Compliance Corner article, the Abbott quality VP names seven reasons why device-makers screw-up management reviews.)

In the end, "the most important thing that should come out of a management review is that the company is a transparent organization," Wilkins said. "Transparency is critical. During the meeting, firms should be able to identify the issues, discuss the issues, and tackle the issues before they become an even bigger problem."

To get the very most out of management reviews, manufacturers should talk, at a minimum, about five specific things, she said.

Meeting attendees should discuss:

1. Resources. "First and foremost, management reviews should give you an indication of your resources," Wilkins said. "Can you

QSR & Management Review

Management review – Sec. 820.20(c) of FDA's Quality System Regulation – directs company executives to appraise "the suitability and effectiveness of the quality system at defined intervals and with sufficient frequency according to established procedures to ensure that the quality system satisfied the requirements of ... the manufacturer's established quality policy and objectives."

While management reviews are mandated by the QSR, the regulation is flexible, allowing firms to decide what should be discussed during the meeting.

determine your resources based on data? You should be able to. And you should be able to determine how you're executing your resources if you're measuring the right things. You should be able to see if you have the right number of resources assigned because you should be seeing signals. If you're measuring the right signals, you'll be able to understand whether you have the right skillsets in place."

2. Products. "All manufacturers monitor their products. Your measures, triggers, data and metrics should give you a signal of product performance," Wilkins said. "How a device is performing is an indicator – and there's going to be not one, but several indicators – that should show how your products are doing in the market. And ask yourself: If you're not measuring product by a family or individually, are you falling short?

"You should be able to detect product issues; they should be visible and there should be a discussion about those issues. That will give you a profile over time of that product, because nothing stays the same.

"Also, talking about new products during management reviews is important. How closely and aggressively are you monitoring those new products? Because you're not going to have the historical data to ensure that they are performing well."

3. Processes. "Just like with products, you'll get signals on your various processes. And because things change over time, you'll need to achieve a profile for your processes that can be shared during management reviews," Wilkins said.

4. Customers. "In your management reviews, you should have a good understanding, to some extent, of the level of satisfaction of your customers," Wilkins said. "For example, for a certain product, are you constantly having a lot of complaints or issues, and if so, do you think the customer is satisfied?

"Or, if you're paying attention to the voice of the customers – you're getting feedback; your marketing and salespeople are out there talking to people. Is that information brought into the meeting? What are the issues that the customers are facing? Those are things that your data and management reviews should highlight, maybe indirectly and in some cases, directly."

5. The Quality System. "Yes, your firm's quality system should meet requirements, but more important, is it an efficient and effective process? You'll want to discuss that," Wilkins said. "And agility – is your quality system agile and mature? Agility factors in because making a change can be difficult – it doesn't matter if your firm is large or small – but if you have good, knowledgeable people that are making good decisions and you have good processes, and good data, you should be able to adjust and over time have a mature quality system.

"Maybe at one point in time you achieved a mature quality system, but that doesn't mean you always stay there. It takes work. There can be changes in people, changes in product materials and changes in components. There are many things that can shift. Just make sure that your data is giving you a picture of how mature you are at any given point in time."

Published online 09/21/17

US FDA Updates Online Device Export Tracker

ELIZABETH ORR elizabeth.orr@informa.com

Manufacturers seeking export documents to sell medical devices overseas will need to give US FDA more information before earning certification, agency staff said during a Sept. 19 webinar unveiling the latest revisions to the CDRH Export Certification and Tracking System (CECATS).

Specifically, CECATS will no longer accept applications that do not include a "yes" or "no" response to a question about a firm's most recent FDA inspection. Adding an exact date isn't mandatory, but could help speed issuance of a certificate, FDA staff said.

Applications also need to identify each device's legal manufacturer, as well as any contract manufacturers. Re-labelers may be listed as manufacturers if they're registered with FDA, but there's no need to list component manufacturers, Ethny Obas, FDA internal compliance officer, said.

Obas admitted the changes might mean more up-front effort for manufacturers seeking certification to export devices, but said the adjustments would ultimately save time by limiting the number of times FDA and manufacturers need to go back and forth.

In another change, the CECATS system now allows users to save and log off during data entry even if an error message displays. Further, the update removes some irrelevant categories from the form and prevents submission of applications that include inactive devices. It also no longer displays any inactive establishment history. In addition, CECATS now features a modernized interface, simplified navigation and fewer acronyms, according to agency staffers.

The update also added the option for users to include an alternate email address, which Obas said could help communications with device manufacturers. "Sometimes the person formally in charge of the account may be the CEO, but there's a regulatory affairs person in charge of actually coordinating export documents," he said. "The update allows CECATS notifications to be sent to both of their email addresses."

Several webinar attendees asked whether the revisions included expanding the page limit on certificates for foreign governments. The limit remains at 25 pages, though FDA staff indicated more space might be offered in the next update.

Introduced in 2012, CECATS lets manufacturers request certificates of regulatory status that are often needed to sell devices outside the US. The system is voluntary, and paper applications for export documents can still be filed. Forms that can be requested via CECATS include the Certificate to Foreign Government (CFG); Certificate of Exportability 801(e)1 and 802; Non-Clinical Research Use Only Certificate; and the Export Permit Letter and Simple Notification.

The updated website aunched Sept. 26 at https://www.access.fda.gov/oaa/. Manufacturers can email cdrhcecats@fda.hhs.gov for help.

Published online 09/19/17

GERMAN VOTE 2017: Business Must Wait As Limboland Merkel Faces Hard Coalition Choices

ASHLEY YEO ashley.yeo@informa.com

The most obvious loser on German election day 2017, CDU leader Angela Merkel saw her CDU/CSU coalition tumble to its second-worst showing in a national election since 1949. But the Martin Schulz-led center-left SPD went one better – achieving its worst showing since the founding of the Bundesrepublik.

For German medtech, it is all to play for and rather too soon to make any plans, given the coalition talks to come.

The provisional results last night showed the CDU/CSU losing 8% of its vote, on 33%, and the SPD crashing to just over 20% – meaning the two big parties' share of the national vote has waned to 53% in 2017, where it was about 81% in 1987. Germany has changed over time, but the 2017 outcome was a shock to the system. (Check out results and reactions, @ashleypyeo)

In a newly-divided country, the right-wing AfD emerged as the surprise package, actually winning – albeit narrowly – the eastern most state of Saxony, and securing 12%-13% of the national popular vote. Indeed, all the smaller parties gained ground – the coalition-candidate Greens and the left wing Die Linke attracted high-single-digit outcomes.

Jubilant before his supporters, FDP leader Christian Lindner rejoiced at bringing liberal politics back into the Bundestag – in 2013, the FDP was erased from the political map for the first time ever – paying the price for a 2009 coalition with the Conservative center perhaps. Now with some 10-11% of the vote, the "business party" will be the holder of some key portfolios in what is the best bet for now – a so-called "Jamaica coalition" (CDU/CSU, Greens, and the FDP).

In 2009, the FDP's Rösler and Bahr ran the health ministry, and did much to raise its profile. From a business sense, a repeat scenario would be all to the good in 2017-21. CDU health minister Gröhe seemed to lose impetus in the second half of his four-year term, and it would be no surprise were Merkel to replace him. *(Also see "Germany Votes: But What Will Change For Health Care, Medtech Post-Election?" - Medtech Insight, 19 Sep, 2017.)*

WEAKENED CDU/CSU STILL IN THE BOXSEAT

Impressively, just a few hours after the 6pm close of voting, Merkel – who secured her fourth term as chancellor, matching the performance of former chancellors Konrad Adenauer and Helmut Kohl – was on a TV discussion panel (ARD's *Berliner Runde*) with the other leaders, chastened by the collapse in her vote, but crucially able to claim that only the CDU/CSU could form a new government. An evidently affronted Schulz blamed Merkel for their joint collapse, saying she had presided over a political vacuum that served to assist the far left and far right. People are already questioning Merkel's appetite and strength to see out the new Parliament.

Shutterstock Andrey_Popov

Principally she is being blamed for the rise of the populist anti-immigrant AfD party, after her widely criticized 2015 refugee policy. The right-wing party enters Parliament for the first time, having only been formed in 2013 on an anti-EU ticket. Lindner calls it the "protest party." The pro-EU FDP had wanted to be third-largest party, pre-vote, but Lindner has said the FDP is ready to play its part in ensuring the political stability of Germany. But expect heated Green/Liberal debate over climate change policy.

Germany has enough on its hands, but as the *de facto* chief guardian of the EU and its principles, the post-election panel debate extended to Brexit. Schulz is strongly opposed to the two-year additional withdrawal transition proposed last week by UK Prime Minister May. *(Also see "UK Begins Brexit Inquiry On Devices, Pharma Supplies" - Medtech Insight, 22 Sep, 2017.)* The EU/UK Brexit talks enter round four in Brussels today.

The next stage for Germany is "analyzing the results." With its low vote, the SPD immediately ruled out participating in a coalition and will go into opposition. Merkel is keeping the door open for them, however: An SPD-coalition is a mathematical possibility, she stressed. "We live in stormy times," she said, acknowledging the difficulties of either coalition ostensibly available to her. She is "generally confident" of delivering a stable government – whether that is "by Christmas," as suggested by the *Berliner Runde* anchorman, depends on the progress of negotiations of the coming weeks.

Published online 09/25/17

UK Begins Brexit Inquiry On Devices, Pharma Supplies

ASHLEY YEO ashley.yeo@informa.com

The UK's vote to leave the EU means that decisions will have to be made regarding medtech supplies and the associated regulations that will apply after the scheduled exit date of March 29, 2019.

The UK medical device and diagnostics industries have been clear so support continuity with the current EU systems, which UK stakeholders – chiefly the Medicines and Healthcare products Regulatory Agency (MHRA) – have done much to help build. A letter to this effect was sent to David Davis and Michel Barnier, the head UK and EU Brexit negotiators, respectively, by the UK medtech industries in mid-September. *(Also see "Keep Regulatory Status Quo Post-Brexit, Industry Tells Negotiators" - Medtech Insight, 15 Sep, 2017.)*

But a full inquiry has now been launched by the UK House of Commons select committee on health to get information and feedback from all stakeholders. The inquiry on "Brexit – medicines, medical devices and substances of human origin inquiry" will take submissions until October 26, 2017, and public hearings will be held, provisionally in November and December.

The effort's aim is to gather information on the best ways to guarantee the safe and effective supply of medicines, medical devices, medical products and substances of human origin in the UK. The committee is also focused on giving certainty to patients, the NHS and the UK's life science industry about the regulatory arrangements after Brexit, and delivering a smooth transition towards them.

MAY'S WORDS ON BREXIT ADD TO ONGOING DEBATE – BUT NOT MUCH MORE

Transition was also on the minds of the UK's political leaders on Sept. 22, when Prime Minister Theresa May gave her second major public speech on her Brexit position in Italy. She spoke of a proposed "implementation period" of around two years, which would give certainty to UK businesses, and others, and allow EU27 migrants to continue to newly arrive in the UK subject to a "registering" requirement. It would theoretically mean a transition period lasting until March 2021 – but it would first need the agreement of all parties.

No formal "divorce bill" was broached by May in any detail – the point of a speech lacking in details so long after Article 50 was invoked was lost on many. The prime minister said merely that the UK would "make an ongoing contribution to cover our fair share of the costs involved" and would honor commitments made during "the period of our partnership." In short, while the speech bears scrutiny, it does little more than continue the ongoing debate.

INQUIRY'S SCOPE

The UK government also wants to use its inquiry to size up the major implications for the future of medical research and development.

Specifically, the scope of the inquiry extends to:

- The key considerations that arise for companies, health-care services and regulatory bodies in the UK because of the country's withdrawal from the EU;
- Measures to minimize or eliminate adverse impacts on patients and the public, and to maximize opportunities to enhance services;
- Alternative arrangements for the regulation of medical devices, medicines, medical products and substances of human origin that could be introduced, together with the respective opportunities, risks and trade-offs;
- Identifying how much time is needed for a smooth transition to any new arrangements (i.e., is it best to move directly to any new arrangements post-March 29, 2019, or are transitional arrangements needed?);
- How will withdrawal from the EU affect the UK's ability to influence international standards in life sciences?;
- The arrangements needed to ensure the safe, effective and timely supply of medical radioisotopes over the short-, medium- and long-term; and
- The implications for medical R&D, and how timely UK patient access to innovations developed within or outside the UK might be impaired.

Published online 09/22/17

Leveraging mHealth Data For Product Development: FDA-Supported Action Plan Released

FERDOUS AL-FARUQUE danny.al-faruque@informa.com

A working group of US FDA and industry stakeholders say mobile health technology holds huge potential for advancing medical research, particularly as tools to collect and share data. A new action plan published by the group proposes several steps to help reap that potential.

The Duke-Margolis Center for Health Policy unveiled the report Sept. 15, which lays out recommendations falling under five broad themes :

1. Establishing a "Learning mHealth Research Community" tasked with researching patient and consumer-facing mHealth technologies and how they can help generate useful data;
2. Developing research designs using open-sourced industry standards that rely on mHealth data to help companies speed products to market;
3. Ensuring industry has access to well-characterized, standardized, and robust user-generated health data from mHealth products;
4. Using mHealth technology to gather patient data and to ensure patients have access to the data from research they participate in; and
5. Promoting study participation in medical research through mHealth technology.

The working group includes top FDA and industry officials, among them: Bakul Patel, associate director for digital health at FDA's device center (CDRH); Gregory Pappas, associate director of the National Evaluation System for health Technology (NEST) at CDRH; Seth Clancy, senior director of global health economics and reimbursement at Edwards Lifesciences; and John Mattison, a chief health information officer at Kaiser Permanente.

The report notes that while there have been great technological leaps in tracking patient outcomes, a wide gap remains in the understanding patient treatments and long-term outcomes that can be narrowed with mHealth.

Shutterstock: Andrey_Popov

"Mobile health (mHealth) apps and wearables, particularly those that collect patient- and consumer-generated health data, can fill some of these data gaps by providing real-world, more meaningful, high frequency, and/or longitudinal data," they state. "The recommendations in this action plan are focused on improving the ability to efficiently collect and use [real-world data] from patient/consumer facing mHealth apps and wearables that have been made for clinical purposes or consumer use, in order to reuse these data as part of real-world evidence (RWE) generation for medical treatments and products."

SHARING DATA, DEVELOPING STANDARDS

The report urges collaboration between manufacturers and other stakeholders. Christina Silcox, a research associate at Duke-Margolis who coordinated the action plan efforts, acknowledges that manufacturers don't generally like to share research data. However, she told *Medtech Insight* that there are opportunities in the pre-competitive space where firms can work together without compromising business interests.

"I can understand the business reasons for [not wanting to share data] … but everybody understanding what works and what doesn't work is an advantage to everybody," she argues.

Silcox says the report will be integrated into other real-world evidence research that Duke-Margolis is conducting.

"When we were doing this report we really felt like mHealth could avoid some of the problems that other real-world evidence had," said Silcox. "If we get down on the ground floor, we could say interoperability is really important, common definitions are really important, this is the kind of information we need to make it useful for research. But the idea is that you'd be able to combine that with other real-world evidence [research] because the likelihood of mHealth data completely by itself being useful to research would be for very specific cases."

Silcox notes that there are many organizations already doing good work on mHealth research and standards, and doesn't want to start from scratch. However, she says, the Learning mHealth Research Community concept could be a

resource that helps centralize knowledge gathered by multiple organizations under one roof, streamlining access to that information by companies.

"We found that people don't know about all the other efforts that are happening," said Silcox.

Having all the information in one place also researchers see where knowledge gaps remain. Such a community would also give researchers an opportunity to discuss and develop consensus on mHealth research tools, standards and definitions.

Silcox says there would have to be a central group that manages the learning community proposed by the action plan, and Duke-Margolis is looking for interested parties and organizations that could take on that role.

While Duke-Margolis "would certainly have interest in that" there are other organizations, Silcox says, who may be better positioned to play such a role more easily.

A TOOL FOR REAL-WORLD EVIDENCE

Generating shared-use real-world data has been a major push for FDA, which has championed the NEST real-world evidence program to support both post-market surveillance and pre-market approvals. The agency has fought for funding and industry support to promote the concept of RWE and creation of NEST. *(Also see "Applying Real-World Device Data: US FDA Finalizes Its Thoughts" - Medtech Insight, 30 Aug, 2017.)*

CDRH Director Jeff Shuren has been a key proponent of the concept. At Duke-Margolis' unveiling of the action plan, Shuren said mHealth technology will likely play a pivotal role in how sponsors collect patient data to support approval of their products.

"We see mHealth technology as critically important to the work that we do," he said. "[It's] a really good source of real-world data... [it gives us] the opportunity to measure things that are important to patients."

And he says gathering data on patient outcomes during day-to-day routines outside the clinical setting could be useful in helping companies develop better devices and drugs.

"If you really want to know what technology does, you have to study it in the wild," he added when speaking about the new NEST program.

Shuren also touted the agency's focus on novel "medical device development tools" (MDDTs) that could help accelerate the path to market for devices based on mHealth-collected data, new statistical models and patient-preference data.

Shuren said FDA's focus is to ensure MDDTs are "regulatory grade." where they show new outcome measures are good enough to support a product's approval. To that end, some mHealth technologies could be used to generate some of the outcome measures that MDDTs evaluate, he noted.

While FDA only recently published an MDDT framework, Shuren said the agency is very close to qualifying the first such tool. *(Also see "Expanding The Medtech Toolbox: US FDA's 'Medical Device Development Tools' Program Rolls Out" - Medtech Insight, 18 Aug, 2017.)*

"mHealth gives us a tremendous opportunity not only to better understand perspectives of patients when they're out there in their day-to-day lives but also as a way to engage them… not just assessing technologies out there but help us in terms of technologies coming to market, essentially creating patient scientists," he added.

Maybe one of the most difficult issues in medical research is obtaining informed consent from patients and following up with patients in the long term after getting consent to gather data. Shuren is optimistic that mHealth technology may make that process easier and, as a bonus, allow physicians to better monitor their patient's condition.

"mHealth and all the things we're doing to have a more systematic approach in our collection and use of real-world data...has huge implications for health care generally and in the medical device space, it will change the way we bring technologies to market, how we understand them and how we have the right safety net in place," added Shuren.

CONSUMER-GRADE DEVICES

Using consumer-grade mHealth devices for medical research does raise a question of how useful the data will be to support FDA's regulatory review process. Silcox notes mHealth data can be used to help evaluate devices for reasons beyond reviewing products for regulatory approval. The action plan proposes researchers and mHealth companies could partner to develop a "stepwise validation" process to explore clinical outcomes.

"For example, a pivotal trial for a device may use mHealth data as an exploratory outcome (such as daily activity level as measured by a *Fitbit Alta*)," states the report. Positive correlation of the data with a widely used primary clinical outcome measure (such as the traditional six-minute walk test) could support the validity of the use of the mHealth data as a secondary outcome in a subsequent pivotal trial of another device for a similar indicated population.

"If the positive correlation persists and it is deemed to be clinically appropriate, the mHealth data can be considered as one of the co-primary outcomes or a component of the composite primary outcome in subsequent pivotal studies for devices," adds the report.

Shuren echoed these sentiments when speaking to *Medtech Insight* after the meeting.

"I think we heard from some of the comments today that you don't have to start with going for one of the big-ticket items; you can start at another level," he said. In some cases, Shuren notes that consumer-grade products could be used in investigational studies that provide information that then leads to clinical research down the road to support a medical device approval.

He emphasized that there are different requirements from the agency depending on the product being reviewed.

"If you're using a technology to gather information and even if that is for gathering information for purposes of assessing a device, that's not a medical device, so we don't regulate that technology," said Shuren. "But if you are using a technology to assess a technology for purposes of getting it approved, you want to make sure it is accurate enough and we're going to be able to rely on the data that's generated. That is really the key point."

Part of the new action plan also emphasizes the development of standards. Shuren said there are different levels of standards, including data standards and

interoperability standards, that FDA is highly invested in. Ultimately, he says the goal is to develop more confidence in the data generated by mHealth devices.

While these standards are being developed, he says there are other ways to increase confidence in mHealth products.

"For example, when we deal with sensors today, you may have a sensor that, in of itself, is not great but if you take three of those sensors you can triangulate the information and now you have a great sensor," said Shuren. "You can do the same thing with the data."

"Keep in mind for these mHealth technologies, depending upon their use, they're just part of the bigger picture," added Shuren. "You're using it for information, you have lots of other sources of information; we don't look at this in a vacuum. It now becomes how do we link up those different sources."

Published online 09/19/17

CMS Seeks Input On New Directions For Innovation Center

SUE DARCEY sue.darcey@informa.com

The US Centers for Medicare and Medicaid Services is setting a new direction for its Innovation Center, asking stakeholders – including providers, clinicians, state health officials, patients and patient groups – to provide the agency with some ideas for possible new payment models that focus on providing quality care to patients, as well as competition and transparency.

"We will move away from the assumption that Washington can engineer a more efficient health-care system from afar, or that we should specify the processes health-care providers are required to follow," CMS Administrator Seema Verma wrote in a Sept. 19 editorial in the *Wall Street Journal* about the request for information (RFI) for the Innovation Center.

However, some members of Congress who called for the original formation of the CMS Innovation Center -- known as the Center for Medicare and Medicaid Innovation (CMMI) during the Obama administration – are not happy with Verma's and US Health and Human Services Secretary Tom Price's effort to take CMMI in a new direction.

"Today the Trump administration started an end-run around the democratic process to radically change seniors' Medicare and raise their health costs. Beginning down this treacherous path is a clear sign that Secretary Price is betraying Donald Trump's campaign promise not to touch Medicare or Medicaid," Sen. Ron Wyden, D-Ore., said in a statement.

CMS also seems to be focused on scaling back some value-based payment models that orthopedic and cardiac specialists have begun to participate in during the last two years. The agency issued a proposal Aug. 15 to reduce the number of geographic areas participating in a "comprehensive care for joint replacement" payment program, and to eliminate its "cardiac rehabilitation" incentive pay program. *(Also see "Could CMS Changes To Bundled Pay Models Stifle Medtechs' Value-Based Pay Plans?" - Medtech Insight, 16 Aug, 2017.)*

RFI FOR NEW IDEAS FOCUSES ON COMPETITION, VOLUNTARY MODELS

In its RFI, which takes the form of an anonymous survey, CMS says it will approach a new model design keeping in mind the following guiding principles:

- Choice and competition in the market: Promoting competition based on quality, outcomes and costs.
- Provider choice and incentives: Focusing on voluntary models, with defined and reasonable control groups or comparison populations, to the extent possible, while reducing burdensome requirements and unnecessary regulations to let physicians and other providers focus on providing high-quality health care to patients.
- Patient-centered care: Empowering beneficiaries, their families and caregivers to take ownership of their health, and ensure they have the flexibility and information to make choices.
- Benefit design and price transparency: Using data-driven insights to ensure cost-effective care that also leads to improvements in beneficiary outcomes.
- Transparent model design and evaluation: Drawing on partnerships and collaborations with public stakeholders, and harnessing ideas from a broad range of organization and individuals.
- Small-scale testing: Testing smaller-scale models that may be scaled up if they meet the requirements for expansion under provisions in the Affordable Care Act, and focusing on interventions, rather than on specific devices or equipment.

Further, the Innovation Center wants to test models that are centered on alternative payments, consumer-directed care, physician specialties, prescription drugs, Medicare Advantage, state-based models and local innovation, mental and behavioral health, and program integrity.

Published online 09/21/17

Essure Court Cases Move Ahead, Clear Legal Obstacles

A lawsuit alleging **Bayer AG** is responsible for injuries experienced by women using the company's Essure contraceptive device took a step forward in California state courts Sept. 20 as plaintiffs filed a revised complaint against the company alleging negligence, liability, fraud and breach of warranty. Bayer says the allegations are false.

The women allege Essure caused a range of problems including excessive pain, internal perforations and heavy bleeding. Similar complaints already led US FDA to modify the product's labeling to include a black-box with a checklist of safety warnings that obstetrical and gynecological providers must discuss with patients.

The coordinated proceedings in Alameda County Courts include at least 3,000 complaints with more still being filed, plaintiff attorney Elizabeth Graham, Grant & Eisenhoffer, says. The lawsuits are being heard in California because both Essure developer **Conceptus Inc.** and current manufacturer Bayer have corporate offices in the state.

Two rulings from California Superior Court Judge Winifred Smith have been key in permitting the cases to proceed, Graham said. The first established that women could not have known Essure posed a risk prior to a 2015 FDA hearing, which allowed some plaintiffs to file claims that would otherwise have been beyond the two-year statute of limitations. *(Also see "Essure Panel Stresses Need For Patient Follow-Up, But Stressed-Out Patients Say, 'Recall It'" - Medtech Insight, 28 Sep, 2015.)*

The second determined that the preemption defense, which typically blocks patients from suing manufacturers of PMA-approved products, did not protect Bayer from all claims against Essure. That's because some of the alleged negligence occurred not during the approval process, but after the devices hit the market, Graham said.

"The crux of our allegation is not the approval of the device itself, but that Bayer and Conceptus did not report adverse events," she explained. "As a company, they have an obligation to report problems with the device." She says she's seen "tens of thousands of reports" of adverse events tied to Essure that didn't go to FDA in a timely manner, and has asked Bayer for access to its complaint database to see if there might be others.

"During the time period that these weren't being reported, the company was still representing the device as safe and effective," she said. "Especially in California, if you have a duty to tell the truth, it has to be the whole truth."

The federal court of appeals that includes California in its jurisdiction (Ninth Circuit) has previously allowed liability claims based on allegations of a lack of adverse-event reporting to proceed. And in 2014, the US Supreme Court declined to hear a case that could have allowed it to weigh in on that approach. *(Also see "Preemption Questions Persist: Supreme Court Doesn't Take Bait In Medtronic Case" - Medtech Insight, 2 Jul, 2014.)*

Graham believes Conceptus initially "buried" the adverse event reports as part of its efforts to sell itself and the product to a larger manufacturer. Bayer paid $1.1b for Conceptus in 2013. *(Also see "Bayer completes $1.1bn Conceptus buy" - Medtech Insight, 6 Jun, 2013.)*

Bayer spokeswoman Courtney Mallon disputes Graham's allegations. She says 25 Essure cases have been dismissed or narrowed based on preemption, including some claims in Alameda County. In addition, the company says it did not fail to report adverse events.

> "Such false statements, which have no basis in fact, do a disservice to women who are considering Essure as a means of permanent contraception," Bayer spokeswoman Courtney Mallon says.

"Such false statements, which have no basis in fact, do a disservice to women who are considering Essure as a means of permanent contraception," she said. "Bayer will vigorously defend against all remaining claims in court."

The cases are yet to get a court date, but discovery is proceeding, Graham says. She hopes to go to trial within the next year.

In other recent Essure news, Bayer is removing the product from the European market, and it is no longer sold in Canada or Brazil. Mallon stressed that the withdrawal is "unrelated to product safety or efficacy," and the device remains on the market in the US. *(Also see "Bayer Halts Essure Sales In EU As US FDA Relies On Study, Patient Warnings" - Medtech Insight, 20 Sep, 2017.)*

Graham, the plaintiff attorney, speculates more than commercial concerns are behind Bayer's reluctance to take the device off the US market.

"They don't want any hint of an admission of liability because of the thousands of women they injured," she said. "And in the US, women have a right to go to court and get redress for their pain and suffering. I'm extremely disappointed they won't make the same decision inside the US."

Bayer, however, says it has no plans to stop selling Essure in the US.

"Bayer stands behind the positive benefit-risk profile of Essure, the only FDA-approved non-incisional option available to women for permanent birth control," Mallon said. "The safety and efficacy of Essure is supported by more than a decade of science and real-world clinical experience."

Published online 09/22/17

Positive Long-Term Data Plug Doubts Over PFO-Closure Stroke Benefits

REED MILLER reed.miller@informa.com

Results of three clinical trials, published in the *New England Journal of Medicine*, support percutaneous closure of patent foramen ovale (PFO) to prevent recurrent stroke after a cryptogenic stroke, which could lead to a change in the professional guidelines on the treatment of these patients and help the companies trying to market PFO-closure devices.

On Sept. 14, *The New England Journal of Medicine* published long-term results of three clinical trials comparing PFO-closure with a transcatheter device and medical therapy to medical therapy alone: RESPECT, REDUCE, and CLOSE trials.

All three trials showed that closure of the PFO – a hole in the heart's septum caused by a congenital defect in about 25% of people that can be seen by transesophageal echocardiography – is associated with a lower rate of recurrent ischemic strokes than medical therapy alone.

The positive outcomes mark a breakthrough for researchers and manufacturers that have been working for two decades to show that PFO-closure can reduce the risk of an embolism passing through the heart and causing another stroke in patients who already had a cryptogenic stroke – a stroke that could not be definitively attributed to any specific cause. *(Also see "Gore's PFO Closers REDUCE Recurrent Ischemic Strokes By 77% In Trial" - Medtech Insight, 2 Jun, 2017.)*

Neither the earlier follow-up from RESPECT nor the four-year follow-up from the PC Trial showed a statistically significant benefit for PFO-closure in patients following cryptogenic stroke. And because the trials failed to show a clear benefit to PFO closure, in July 2016, the American Academy of Neurology updated a practice advisory stating "Clinicians should not routinely offer percutaneous PFO closure to patients with cryptogenic ischemic stroke outside of a research setting."

"This [new data] will come as a surprise to many doctors. When the first three trials were reported in 2012 and 2013, each of them was, by itself, not positive," the lead author of RESPECT, Jeffrey Saver of the University of California, Los Angeles, told *Medtech Insight*. The three trials he referred to are the earlier results from RESPECT, the PC Trial, and the 909-patient CLOSURE-1 trial of NMT Medical Inc.'s STARFlex closure device.

"People got the impression that this treatment might not be beneficial and excitement about it diminished in the practice community, but the fact that all the numbers were running in the right direction was not fully appreciated. And many people are going to be pleasantly surprised that the longer observation in RESPECT and two newer trials have now returned positive," he explained. "There was a wave of enthusiasm for closure from 2000 to 2005 or so and a lot of people thought it was the best thing to do. Then when [the earlier follow-up from] these trials came out, there was a wave of disappointment and disillusionment and a lot of people thought it was not going to be a productive path, but now I think we'll see a wave of enlightenment where people recognize that it is a beneficial approach in certain patients."

The lead author of the AAN practice advisory, Steven Messé of the University of Pennsylvania, told *Medtech Insight* in an email:"The new data is very encouraging and I do think that the existing guidelines need updating. The AAN is currently working to update the guideline on this topic."

RESPECT FINDS PFO-CLOSURE BENEFIT AT SIX YEARS

St. Jude Medical Inc. /Abbott Laboratories Inc.'s *Amplatzer PFO Occluder* became the first device approved for reducing recurrent stroke in patients with a PFO and a history of stroke in October 2016, but though both trials supporting Amplatzer failed to show a statistically significant reduction in stroke recurrence in the primary intent-to-treat analysis – the 980-patient RESPECT trial, sponsored by St. Jude, missed its primary intent to treat analysis after a median follow-up of 2.1 years and the 414-patient PC trial failed to show a benefit of the device over a mean follow-up of about four years. *(Also see "Advisors Give Lukewarm Endorsement Of St. Jude's PFO Occluder For Stroke" - Medtech Insight, 25 May, 2016.)*

Amplatzer PFO Occluder

Photo credit: Abbott Laboratories

The new analysis of RESPECT in *NEJM* includes results from 980 patients from 69 sites followed for a median of 5.9 years.

All the patients were 18 to 60 years old, had a PFO, and had suffered a cryptogenic ischemic stroke. They were randomized to PFO-closure with Amplatzer or antithrombotic medical therapy, including aspirin, warfarin, clopidogrel, or aspirin combined with extended-release dipyridamole. The study included 3,141 patient-years in the PFO closure group but only 2,669 patient-years in the medical-therapy group because of the higher dropout rate in the medical-therapy group.

In the intention-to-treat population, recurrent ischemic stroke occurred in 18 patients in the PFO closure group and in 28 patients in the medical-therapy group, for a rate of 0.58 events per 100 patient-years in the closure group and 1.07 events per 100 patient-years in the control group and a hazard ratio of 0.55, $p = 0.046$.

Recurrent ischemic stroke of undetermined cause afflicted 10 patients in the PFO closure group and in 23 patients in

the medical-therapy group (hazard ratio, 0.38; p = 0.007), but venous thromboembolism was more common in the PFO closure group than in the medical-therapy group. The relative difference in the rate of recurrent ischemic stroke between the two groups was large – 45% lower with PFO closure – but the absolute difference was small – just 0.49 fewer events per 100 patient-years. "Nonetheless, the cumulative absolute benefit had clinical relevance, since patients in this trial were younger than the general population of patients who have strokes and thus faced a longer period of risk for recurrent stroke," the RESPECT authors explain in *NEJM*. Based on these results, 42 patients similar to those in RESPECT would have to be treated with PFO-Closure to prevent one stroke over a five-year period, the point out.

The rates of pulmonary embolism were 0.41 per 100 patient-years in the PFO closure group and 0.11 per 100 patient-years in the medical-therapy group (hazard ratio, 3.48) and the rate of deep-vein thrombosis was 0.16 per 100 patient-years and 0.04 per 100 patient-years, respectively (hazard ratio, 4.44). The rate of venous thromboembolism in both groups is greater than what would be expected from a healthy population, suggesting that people with a PFO who have had cryptogenic stroke face a mildly elevated long-term risk of venous thromboemboli.

"In our trial, the lower intensity of antithrombotic therapy, including the less common use of anticoagulant agents, in the PFO-closure group than in the medical-therapy group may have contributed to the higher rate of venous thromboembolism in the PFO closure group," the RESPECT authors explain. They also point out that within the PFO-closure group, patients who had previously had a deep-vein thrombosis were more likely to have a venous thromboembolic event. This subgroup, accounting for just 4% of the PFO-closure group, accounted for a quarter of all the venous thromboembolic events in the trial. This result provides "indirect support for the recent revision to the American College of Chest Physicians 2016 guidelines endorsing lifelong anticoagulation therapy in patients with overt deep-vein thrombosis.

NEW INDICATION FOR GORE'S CARDIOFORM?

Results from 664 patients in the randomized REDUCE trial followed for a median of 3.2 years show that PFO closure with **WL Gore & Associates Inc.** first-generation *Helex* or next-generation *Cardioform Septal Occulder* devices plus antiplatelet drug therapy reduces the risk of subsequent ischemic stroke compared to antiplatelet therapy alone in patients with a PFO who had had a cryptogenic stroke.

The long-term results from REDUCE were previously presented at the European Stroke Organisation Conference in Prague in June. *(Also see "Gore's PFO Closers REDUCE Recurrent Ischemic Strokes By 77% In Trial" - Medtech Insight, 2 Jun, 2017.)*

"Previous trials of PFO closure did not show efficacy in their primary intention-to-treat analyses; however, analyses based on the as-treated populations, follow-up studies, and meta-analyses have suggested that there is a possible benefit from the procedure in lowering the risk of stroke," the REDUCE authors, led by Lars Søndergaard of the University of Copenhagen, explain in *NEJM*. "Unlike those previous trials, the [REDUCE] trial was designed to determine the efficacy and safety of PFO closure followed by antiplatelet therapy, as compared with antiplatelet therapy alone." Also, the trial required antiplatelet agents to be part of the medical therapy, whereas previous PFO-closure trials left the use of anticoagulants in the medical-therapy group up the discretion of the treating physicians, which may have confounded the results and biased the results from the medical-therapy groups in those trials, Søndergaard et al. explain.

"This study demonstrates PFO-closure is a superior therapy to what physicians have been using in the past related to the treatment of cryptogenic stroke patients with PFO and that's what this study was designed for," Jake Goble, Gore Structural Heart Pipeline Leader, told *Medtech Insight*. "What's really unique about these patients is that these are otherwise healthy individuals and you want to make sure there aren't any other known sources of stroke, because its more probably that is what the index event was due to, but if you cross all of those other options off the list and you have a PFO, then these data are suggesting that this is the right therapy for them."

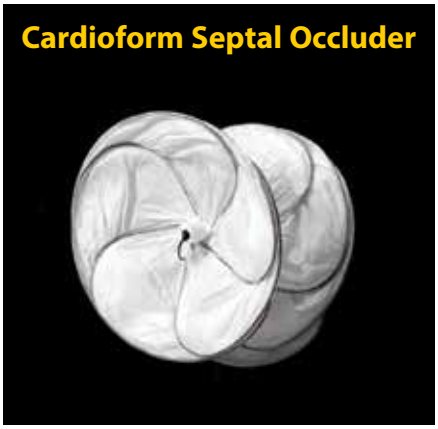


Photo credit: WL Gore & Associates

Cardioform is approved in Europe for PFO-closure, but the company is relying on REDUCE to support US FDA approval for a specific PFO-closure indication. "Now that we have that data, we're going to be interacting with the FDA seeking approval of the device and, on top of that, we'll be able to use this data to help inform private insurance carriers to adjust coverage." Goble said that about a third or the private insurers in the US will not currently cover PFO-closure for stroke. Since almost all of the patients that would get a PFO closure to prevent stroke are under 60, Medicare policy on this procedure is not critical to commercial success of these devices, he said. "If you're 70 years old and having a stroke, it's likely a different reason why you're having a stroke."

In REDUCE,158 of the patients randomized to PFO-closure received a Helex device and 250 patients received the next-generation Cardioform, which was approved by the US FDA for atrial septal defect closures in April 2015. "Once that got approved… we took Helex off the market, because we felt it was better and the data in the trial support that too," Goble said, pointing out that the one-year closure rate with Cardioform was 98% and the one-year closure rate with Helex was 88%.

In the trial, 1.4% of the PFO-closure group and 5.4% of the antiplatelet-only group

suffered an ischemic stroke, (hazard ratio, 0.23; p = 0.002) and 5.7% of patients in the PFO-closure group developed a new brain infarction compared to 11.3% of patients in the antiplatelet-only group (relative risk, 0.51; p = 0.04). Overall, 23.1% of the PFO-Serious adverse events, versus 27.8% of the patients in the antiplatelet-only group (p = 0.22). Based on these results, about 28 patients would need to be treated to prevent one stroke over two years.

Adverse events directly related to the PFO-closure device occurred in 1.4% of the PFO-closure group and 6.6% of that group had atrial fibrillation after PFO closure.

BENEFIT OF PFO CLOSURE WITH ANTIPLATELET THERAPY

The CLOSE trial, funded by the French Ministry of Health, randomized 663 patients 16 to 60 years old who had a recent stroke attributed to PFO, an associated atrial septal aneurysm or large interatrial shunt because previous observation studies showed these characteristics predict a high risk of stroke. The patients were randomized to transcatheter PFO closure plus long-term antiplatelet therapy, antiplatelet therapy alone, or oral anticoagulation drugs.

The investigator-initiated trial was conducted at 32 sites in France and two in Germany beginning in December 2007. Every patient randomized to PFO-closure were treated with one of 11 different PFO-closure devices approved by the trial's Interventional Cardiology Committee and over half of the 238 patients in the PFO-closure group were treated with Amplatzer.

There were no strokes in the 238 patients in the PFO closure group, while 14 of the 235 patients in the antiplatelet-only group had a stroke (hazard ratio, 0.03; p < 0.001), but 14 patients had a procedural complication from PFO-closure (5.9%) and the rate of atrial fibrillation was higher in the PFO closure group than in the antiplatelet-only group (4.6% vs. 0.9%, p = 0.02). The number of serious adverse events did not differ significantly between those two treatment groups. Three of 187 patients in the oral anticoagulants group had a stroke and 7 of 174 patients assigned to antiplatelet therapy-alone group had a stroke.

Extrapolated based on the Kaplan–Meier probability estimate, the CLOSE trial shows the five-year risk of stroke was 4.9 percentage points lower with PFO-closure plus antiplatelet therapy than with antiplatelet

therapy alone, equivalent to one stroke avoided every five years for every 20 treated patients. Among patients in the antiplatelet-only group, patients with both PFO and atrial septal aneurysm had the highest risk of stroke.

The CLOSE authors suggest that the trial showed a benefit of PFO-closure after many previous trials did not, because they restricted the trial to First, we included only patients with a PFO along with an associated atrial septal aneurysm or a substantial right-to-left interatrial shunt. The CLOSE investigators also used a standardized evaluation to define a previous cryptogenic stroke in order to ensure the patients in the trial were unlikely to have a recurrent stroke for a reason other than their PFO. Also, the patients in the trial had fewer vascular risk factors than the patients in previous trials, so they were less likely to have a stroke due to vascular factors.

The authors also point out that CLOSE's control group included patients receiving antiplatelet therapy alone. By contrast, the control groups in previous PFO-closure trials included patients who received either antiplatelet drugs or oral anticoagulants, or sometimes both, according to physician preference, which may have confounded the results.

WHAT CAUSED THE CHANGE IN OUTCOMES?

In an editorial accompanying the RESPECT, REDUCE, and CLOSE papers in *NEJM*, Allan Ropper of Harvard Medical School asks why these trials showed a benefit of PFO-closure after so many trials failed to show a benefit of the therapy.

"It would be simple if the conversion from a negative to a positive outlook with respect to PFO closure could be explained by studying the various antiplatelet and anticoagulant treatments, or the various durations of follow-up among the trials, or the tyranny of a P value of 0.05, as discussed previously by other editorialists, but I found it futile to discover the answer in these details," Ropper writes.

He calls RESPECT "the most provocative" of these three trials because a previous analysis of the same trial based on a shorter follow-up did not show a benefit of PFO-closure in that the entry criteria. "However, the longer duration of follow-up alone is probably not the reason for a change from negative to positive results," Ropper argues. "A hint to explaining the discrepancies in results among the trials may be the stringent entry criteria in the CLOSE trial" because no patient in the PFO-closure group in that trial had a stroke, whereas 6% of the antiplatelet only group had a stroke, whereas REDUCE represents "a middle ground by including patients with a moderate-to-large interatrial shunt but not requiring that patients have an atrial septal aneurysm.

"Therefore, in patients who have had a stroke, are younger than 60 years of age, and have a PFO with characteristics that are highly likely to allow paradoxical embolism to occur, the effect of closure becomes persuasive," he concludes.

Ropper also suggests that the "ill-defined and ill-used term 'cryptogenic stroke,'" is problematic. "All these schemas are circumscribed by the aspects of stroke that are absent, rather than by characteristics that are present and would lead to the conclusion that PFO is likely to be the mechanism of recurrent stroke," he explains. "The evidence for causation of embolic stroke in any given person is, of course, circumstantial (e.g., atrial fibrillation or carotid stenosis), and it seems reasonable that the presence of a PFO and a sizable interatrial shunt should similarly no longer result in the categorization of a stroke as cryptogenic. One conclusion from the six trials described above is that the potential benefit from closure is determined on the basis of the positive characteristics of the PFO rather than on the basis of exclusionary factors that make a stroke cryptogenic. Restricting PFO closure entirely to patients with high-risk characteristics of the PFO may perhaps be too conservative, but the boundaries of the features that support the procedure are becoming clearer."

Published online 09/25/17

Ernst & Young Bullish On Medtech's Fusion With Innovation

MARION WEBB marion.webb@informa.com

Things are looking up for the global medtech industry, but only those companies willing to embrace innovative technologies such as artificial intelligence will come out winners, according to Ernst & Young's annual medtech report, presented today at this year's MedTech conference, hosted by AdvaMed, in San Jose, California.

Last year, the medtech industry grew by 5%, with aggregate revenue from US and European medtech companies hitting $364.4bn, a pace last seen before the financial crisis. This growth was driven by mergers and acquisitions and portfolio optimization strategies, and a continued focus on capital efficiency and research and development investments, according to EY's 2017 *Pulse of the industry* report.

"Medtechs continue to use M&A, collaborations with new entrants and new technology investments to navigate an array of uncertainties," said Pamela Spence, EY's Global Life Sciences leader in a company statement. "To achieve sustainable growth though, medtechs must embrace more data-driven strategies that co-create value for all industry stakeholders and participate in emerging outcomes-driven care delivery platforms that are highly personalized." *(Also see "M&A Analysis: August Activity Cools As The Summer Closes" - Medtech Insight, 7 Sep, 2017.)(Also see "Device Week – The Summer Of M&As, Aug. 21, 2017" - Medtech Insight, 18 Aug, 2017.)*.

Spence noted that companies need to balance internal R&D investments with innovations with the "new, connected economy" – augmented reality (AR), additive manufacturing (AM) and artificial intelligence (AI) *(Also see "Artificial Intelligence Brings Wave Of Future Health Care Innovation – Embrace it or be Left Behind" - Medtech Insight, 28 Jul, 2017.)*.

NEW ERA

"Embracing 'The 4th Industrial Revolution,' which fuses the physical, digital and biological, is a current – not future – imperative," Spence said *(Also see "Virtual Reality: The New Game In Mental Health Care To Improve Outcomes" - Medtech Insight, 22 Jun, 2017.)*.

According to the report, new innovations will continue to drive the medtech industry's growth.

The report noted that additive manufacturing, for instance, allows for developing anatomical models surgeons can use to practice complicated procedures prior to surgeries. *(Also see "How 3D Printing Can Enhance And Expand Medtech Opportunities" - Medtech Insight, 7 Sep, 2017.)* **Stryker Corp.** is among the medtechs that has invested heavily in this space with a dedicated facility in Ireland to create components for several spine and joint replacement products. Stryker and another giant, **B. Braun Medical Inc.** among others, are also interested in using AR to improve the precision and outcomes of surgeries, the report noted.

"Over the next two years, one major trend will be "smart" operating rooms that juxtapose real-time anatomical information with a variety of other types of data," the report stated.

Technological advances in sensors, coupled with advances in artificial intelligence, will broaden the definition of medtech to include digital and data-driven services.

This, in turn, will spell even faster convergence, lowering the barriers to entry for newcomers, especially those that specialize in software-based or other customer-focused services. To succeed in this environment requires that medtechs build flexible business models that balance R&D and external innovation.

Looking at total figures, revenue from US- and Europe-based medtechs climbed to $364.4bn in 2016, up 5% from 2015. This was a significant improvement from 2015, which saw a 3% decline in revenue from the previous year. Also in 2016, net income for these companies climbed a whopping 17% to $16bn, compared with a 20% drop to $13.7bn in 2015. Additionally, R&D spending by medtechs rose 5% to $16bn in 2016.

Companies' focus in prior years on capital efficiency, therapies and delivering better health outcomes means that many of the industry's top commercial leaders are now delivering strong top-line and bottom-line growth, according to the report. Smaller companies and their savvy investors are also reaping the benefits of robust public and private financing.

"As a result, they have – for now – sufficient funds to develop tomorrow's new medtech innovations," the report stated.

According to the report, US and European medtech financing rose 101% in 2016 to $43.9bn, the second-highest total in the past decade. Venture capital financing climbed to $7.7bn, a 23% year-on-year rise and a positive sign for future medtech innovation *(Also see "VC Deals Analysis: Liquid Biopsy Summons Yet Another Top A-Lister" - Medtech Insight, 8 Sep, 2017.)*. However, more than 25% of that total VC funding went to just three privately held medtechs: **Grail Inc.**, **Guardant Health Inc.** and **Verily Life Sciences LLC** (*Also see "M&A Analysis: Grail's Chinese Merger Wraps Up Busy May" - Medtech Insight, 9 Jun, 2017.*)

Ernst & Young predicts that if the public markets grow tougher and US VC's are willing to bet less, more early-stage medtechs may be competing for the same pool of capital.

Arda Ural, Partner Ernst & Young LLP – Life Sciences, Transaction Advisory Services, told *Medtech Insight* that in recent years there has been no shortage of investment capital to go around from private equity and VC funds to go into higher-risk investment.

"Spaces like miniaturization, artificial intelligence, big data analytics, things that would create an outcome-focused, value-based treatment (such as) sensors and robotics is where venture money went in, and, as a result, these companies are looking for bolt-on opportunities to acquire these platform-enabling technologies," Ural said. "You would expect in the next couple of years more of these platform-enabling technologies to come to fruition with some focus on value-generation, outcome and patient focus."

"There is financing for medtechs, particularly those that are developing tools for the biopharma industry, which is eager for novel technologies that either improve drug development or deliver

TABLE 1

Selected Examples Of Digital Deals, 2016-2017

PARTNERS INVOLVED	ANALYSIS
Royal Philips and PathAI	Solution improves the precision and accuracy of routine diagnostic of breast cancer and other diseases using artificial intelligence.
Stryker and Microsoft	Augmented reality-based system integrates multiple types of data to create the operating room of the future.
Medtronic and IBM Watson Health	Next-generation predictive diabetes app that proactively alerts patients at risk of hypoglycemia of an attack hours before it actually happens.
Agfa Healthcare and IBM Wastson Health	Cognitive technologies to improve the accuracy of imaging in multiple disease areas.
Johnson & Johnson (Ethicon) and Touch Surgery	Simulated surgical training program distributed via an app for doctors in remote areas of the world.
Sanofi and Verily	Launch of Onduo, a joint-venture to develop a comprehensive diabetes management platform.
Johnson & Johnson and Verily	Joint venture of Verb Surgical combines robotics, visualization, data analytics and connectivity to create a digital surgery prototype.

Source: EY and company reports

differentiated therapies," John Babitt, Partner at Ernest & Young LLP Life Sciences, Transaction Advisory Services, said. At the same time, he noted, companies must also continue to focus on capital efficiency to maintain or improve future growth trajectories.
The good news is that the global funding pool is expanding, particularly in Asia, which medtechs can tap for their future needs.

China is poised to become one of the leading regions for total equity, as medtechs raised more than $1bn in 16 financings and Asia backers were also actively backing US and European medtechs, participating in three of the year's largest VC rounds.

A new guideline that came out in August by the Chinese government to preserve liquidity in China may restrict capital outflow in the future, but Ural predicts this should not impact tech investment.

By contrast, "It actually encourages investment in technology," he said. "For medtech, we don't see that as a concern at this point, because the guidance encourages investment into high-end technology and participating more in the innovation side of things, which the US is obviously the leader and is projected to be in the near future."

To stay on the road of success, medtechs will need to forge partnerships with a range of stakeholders, including payers and providers, the report noted.

When companies look at these technology capabilities, they realize they cannot build those internally, otherwise they will not be competitive, agile enough," Ural said. Consequently, medtechs looks at tech companies to do a joint venture deal, partnership or acquire the capability and vice versa.

"There is a lot of that experimentation going on," Ural said. He gave the examples of **GlaxoSmithKline PLC** and **Google's** life sciences division Verily, which co-founded **Galvani Bioelectronics**, and **Medtronic PLC** and **Qualcomm's** collaboration on continuous glucose monitors, which Ural described as large-scale pilots to bring technologies to patient solutions *(Also see "Qualcomm: A New Kind Of Medical Device Company" - Medtech Insight, 25 May, 2017.)*.

"And that's the way that medtech companies are looking for differentiation and better outcomes and adding more value to the lifecycle," he said.

He noted that in digital health investment, there were 188 deals in the first half of this year alone with double-digit annual growth.

He noted that while fintech (financial technology) has been ahead of medtech, "I think that medical technology is now challenging fintech in terms of attracting venture capital." Investors are going to be attracted to companies pursuing "incremental innovation by adding to existing products" and "disruptive innovation."

Among the other key findings in the report was the strong deal-making environment – with medtech companies in the US and Europe announcing deals worth nearly $100.4bn, an increase of 46% over the prior 12 months and an industry record.

Looking at the overall life sciences sector through the end of August 2017, the total number of US dollars invested is lower than at 2014-2016 levels, he said. But he pointed out that the medtech subsector has been growing over the last three years, except for 2014.

"The portfolio optimization in our analysis has been going well for medtech," he said. "The same cannot necessarily be told for some of the other subsectors, but medtech seems pretty healthy for on-going and diverse activity. A lot of smaller transactions are adding to this $100bn so far for the year, which is healthy."

That is in stark contrast to the cooling period on the IPO side with European and US companies raising just $547m in IPO capital during 2016-17, which marks an 8% drop over the prior year's total.

"While it's still possible for medtechs to go public, general investor participation now requires strong management teams and products that are not only on the market but demonstrating revenue growth," the report stated.

Published online 09/25/17

Series B Pumps $15m Into Abiomed-Backed Acute HF Start-Up

TINA TAN tina.tan@informa.com

Israeli acute heart failure (HF) therapy firm **Magenta Medical Ltd.** has bulked up its coffers with an additional $15m, following a Series B financing that brought in new investors from Japan and the clinical cardiovascular community.

The latest injection of funds is nearly twice the $8.5m raised by the start-up in previous financing rounds, in which Israeli venture capital firm Pitango and **Abiomed Inc.**, developer of the world's smallest heart pump Impella, were the key investors. These two parties also participated in the series B, together with JAFCO Co Ltd., a leading VC in Japan, and Jacques Séguin, the cardiovascular surgeon-cum-serial entrepreneur better known as the founder of the transcatheter aortic valve replacement firm CoreValve.

In conjunction with this financing, Magenta has also appointed David Israeli as its CEO. Israeli is a partner at Pitango and has served as Magenta's chairman since the VC provided seed funding to the start-up in 2012.

Magenta will use the funds to support an ongoing European clinical trial of the acute HF therapy it has developed, a catheter-based system designed as "non-pharmacological, hemodynamically-based, more physiological" alternative to diuretics.

Diuretics are the current mainstay of therapy for congestive HF patients who are admitted to hospital due to an acute worsening of their condition. These episodes of acute HF, sometimes referred to as acute decompensated HF, are caused by systemic congestion, the retention of salt and fluid throughout the body which elevates systemic venous pressure and further increases the burden on the already weak heart and also on the kidneys. Diuretics are used to increase the production of urine and thus decongest acute HF patients. However, there is a body of evidence that show these drugs do not provide adequate treatment, Magenta told *Medtech Insight*; they are known to have a toxic effect on the kidneys and result in worsening kidney function and hospital readmission, the company said.

Magenta's therapy, on the other hand, does not induce production of urine. Instead, it enhances the ability of the kidneys to perform their original function of removing salt and fluid from the body. "It is important to note that we are not a renal replacement therapy, like dialysis, but a renal optimization therapy," the company underlined. By supporting the body's natural process of expelling this excess fluid, the systemic congestion is reduced in a "safer and faster" way, "allowing for a more stable release of that patient."

The firm declined to provide specific details of how its technology works, but said based on the facts that a catheter is inserted in the venous vasculature and the aim is to literally decompress and reduce the pressure that the kidneys are subject to should give a good indication of the technology's mechanism of action and where the catheter is placed anatomically. The technology also comprises a hemodynamic element, using a flow pump to mobilize blood from one area of the body to another.

The company said it is aware of some other firms in the US and Israel which are also developing at non-pharmacological technologies to treat acute HF. Some take a more hemodynamic approach while others take a neuromodulation approach. Two companies in the latter camp include Minnesota-based Cardionomic, whose technology works by neuromodulating the terminal branches of the cardiac plexus to increase the heart muscle's contractibility, and North Carolina-based **NeuroTronik Inc.**, whose CANS Therapy is a catheter-based cardiac autonomic nerve stimulation system and also works by enhancing cardiac output. Both these companies have some heavyweight backers: **Cardionomic Inc.** has **Greatbatch Inc.** and The Cleveland Clinic among its investors, while **Boston Scientific Corp.** led NeuroTronik's recent $23m Series B funding.

But Magenta told *Medtech Insight* that the specific approach it is using is "very unique" and the Tel Aviv company is "very confident of its therapy's superiority over the competition."

The firm is hoping to complete its European clinical trial and gain a CE mark 18 to 24 months from now. Magenta said it intends to approach the US FDA about its regulatory and clinical plans to gain approval for that market once the company has "a critical mass of data" coming from Europe.

Magenta added that with acute HF being a condition that "can take several shapes and forms," it is looking to expand its portfolio further down the line to develop other products that would address this problem, and be a solution – not a single product – company.

Published online 09/28/17

Magenta Medical's Roll Call Of Heart Entrepreneurs Loved By Medtronic

It is not just Jacques Séguin who has successfully sold a company he started to Medtronic. Magenta's founders, cardiologist Ehud Schwammental and mechanical engineer Yosi Tival, were also in the TAVR space with their previous venture, Ventor, which was acquired by Medtronic for $325m in 2009. Additionally, new Magenta CEO David Israeli had previously worked at Medtronic, holding various business development and marketing roles at the medtech giant.

CONTINUED FROM PAGE 1

Baxter CEO José (Joe) Almeida cited technological and cost hurdles at the time.

"Baxter will not be acquiring any home technology going forward, because we don't believe that what is in the market today is economically feasible," Almeida said in a Goldman Sachs conference call from June 7, 2016, as reported by *Mass Device*.

The company will focus instead on developing new technology with telehealth capabilities to advance another at-home modality, peritoneal dialysis (PD).

Laura Angelini, global general manager for Baxter's Chronic Renal business unit, told *Medtech Insight* that Baxter decided to invest in technologies they believe can have a much broader adoption rate.

"In general, hemodialysis is a more complex therapy [than PD], so our assessment was that there were other avenues to assure patients can perform their treatments at home that we believe are more promising," Angelini said.

Whatever happens, insiders say, the current status quo can't last forever.

In-center dialysis is expensive and limits patients' lifestyles. Trained personnel are in short supply, even as more and more patients need dialysis. Some evidence suggests selected patients have better medical outcomes with HHD, too.

Milad also believes that the current model is inherently unsustainable.

"It gives a poor experience to many patients. And it's economically inefficient. We know there are ways we could be doing a lot better for the patients," he noted.

GROWING MARKET

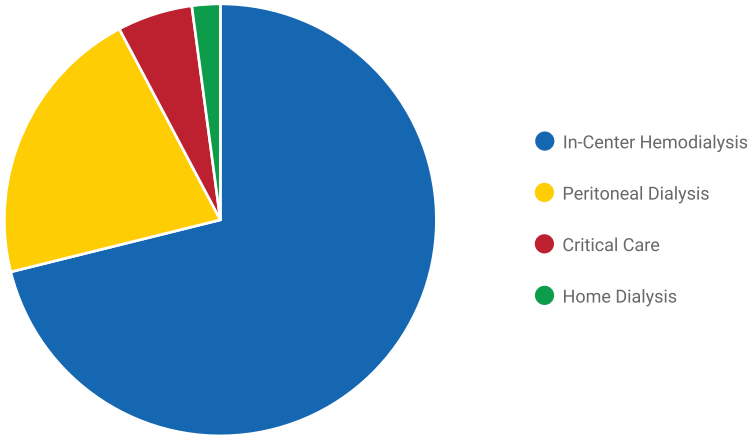
The proportion of patients on HHD varies by country and even by center.

One Australian clinic reported in 2012 that 22% of its patients used the modality, with its head physician estimating that 40% of patients could likely handle it. Still, nationwide in Australia, only 9% of patients received HHD compared to 2% in the US in 2012.

NxStage's 2016 annual report valued the worldwide market for in-center hemodialysis at $10.1bn and PD at $3bn. That compares to a mere $300m (about 13,000 patients) for the global HHD market. An Aug. 8 report on Fresenius by Citi Research was more optimistic, noting a CAGR of 14% in recent years and projected that Fresenius could reach a 4.6% HHD penetration by 2022. (See Figure 1.)

FIGURE 1

Many Insiders Believe Currently Niche Home-Based Modalities Are Set To Grow



Sanford C. Bernstein & Co., LLC. Lisa Bedell Clive. Global Dialysis: A Primer on the Dialysis Products Market (September 17, 2015). NxStage Medical, Inc. data and estimates.

Source: Citi Search

"We're doing minimum dialysis in this country ... you dialyze three times a week and the outcomes are bad," said Robert Lockridge, a retired nephrologist in Lynchburg, Va., and longtime HHD champion.

THE TROUBLE WITH IN-CENTER DIALYSIS

In-center dialysis centers typically schedule the patient for several hours, three days a week; a nurse or technician hooks the patient to a machine and runs it, with the patient being a passive participant.

This setup requires a large capital outlay and skilled staff. The burdensome schedule forces patients into a position of dependence, which can also make it tough for patients to hold down a job. It also requires that patients go without dialysis for an extra day once a week, causing mortality to spike as toxins build up before the next week's cycle—a phenomenon called "Monday-morning syndrome."

Some nephrologists believe that more frequent dialysis -- that removes toxins from the blood more slowly for longer periods, such as in a nocturnal at-home setup -- may lead to better outcomes.

"We're doing minimum dialysis in this country … you dialyze three times a week and the outcomes are bad," said Robert Lockridge, a retired nephrologist in Lynchburg, Virginia and longtime HHD champion.

Lockridge, who helped launch what he described as the first nocturnal HHD program in the US, said, "So we need to change how we're doing it. The only place that that can happen is at home."

BARRIERS TO HHD

However, barriers to wider HHD adoption remain high.

Many nephrologists are untrained in the modality or reluctant to take the road less traveled and are part owners of dialysis centers, which means patients may not be offered the option. For those wanting to go the HHD route, training can take weeks.

For others, the prospect of managing complex, life-saving machinery without immediate medical backup may be overwhelming; as can having to needle one's own fistula, the surgically created artery-vein connection in the arm that allows dialysis access.

Most approved machines also require a caretaker, which rules out HHD for patients who don't have a caregiver at home. Dialysis sessions are typically longer and more frequent at home, reflecting the limits of home plumbing systems. Patients' unreimbursed water bills can be substantial. Many patients who begin HHD give it up and return to in-center care.

Insurance setups can also work against it.

In Citi Research's August report on Fresenius, the authors wrote that covering a week's worth of HHD requires the equivalent reimbursement of 4.5 days.

"While this has not been an issue for the full commercial market, around 80% of dialysis patients are covered by Medicare, and as a result a large part of the market is dis-incentivized to switch to HHD," the authors wrote.

MARKET DRIVERS

That said, there are powerful forces that make HHD look attractive.

With both diabetes and hypertension rates skyrocketing, more patients will experience chronic and eventual end-stage kidney damage. Well over two million patients used dialysis worldwide in 2010, and one model suggests that number will double between 2010 and 2030, according to an article in *ClinicoEconomics and Outcomes Research*.

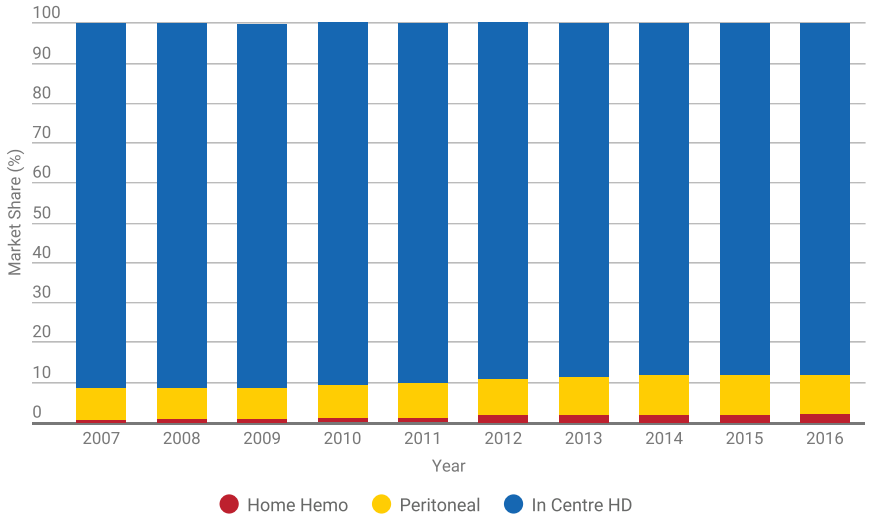
At-home technologies could cut the number of skilled personnel needed to care for dialysis patients at a time when labor accounts for much of the cost of running a clinic and nephrologists are in short supply.

"To treat all these patients 10 years down the road, there will be a need of

FIGURE 2

Home Hemodialysis Gaining US Market Share

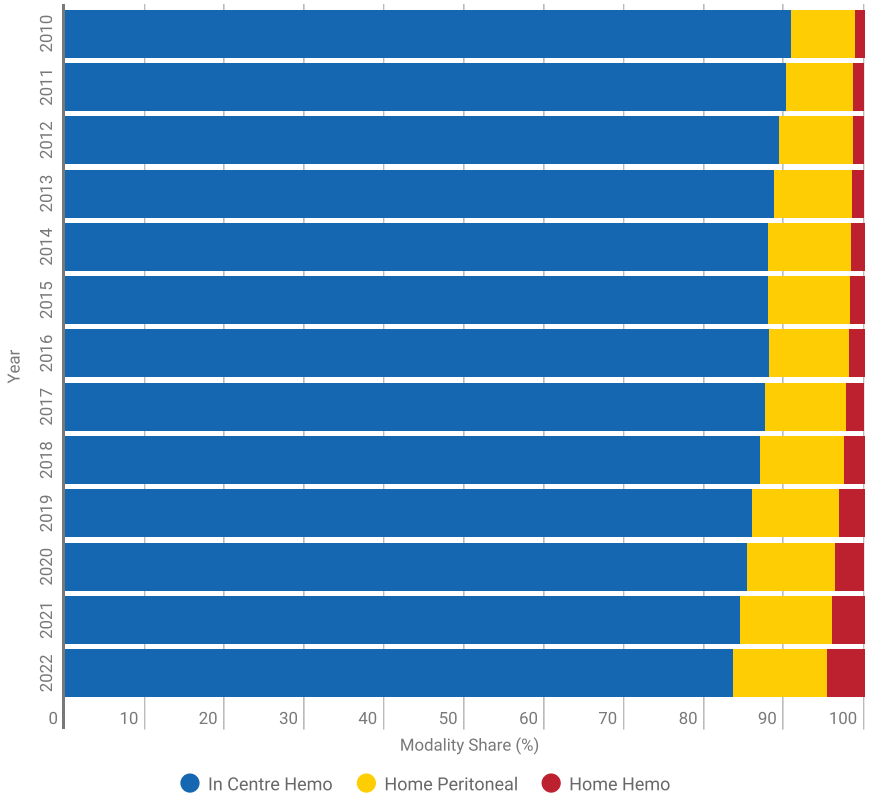
Atop gradual growth in the last decade, Citi research projects future HHD share at 4.6% by 2022. Note: Bar shading not to scale.



Source: Citi Search

FIGURE 3

"Fresenius Medical Care (FMEG.DE). NXTM Acquisition – Homerun Or Homewrecker?"



Source: Citi Research

almost another 30,000 clinics," Angelini said. "The number of nephrologists over the next 10 years will need to grow by 10 percent on a year-by-year basis … How do you pursue technology innovation that is going to allow treatment of more patients, so that a physician that today treats an average of 80 patients, can now treat 200 patients per year?"

She joins others who believe technology can help fill that gap.

According to Citi Research's report, "Both HHD and PD are liked by insurers because of their cost efficacy, with patients needing less direct intervention and often superior clinical outcomes due to more frequent dialyzing." (See Figure 2.)

Another driver of HHD is a younger or more educated patient population wishing to reclaim more control over their schedules, Advent Access' Peh noted.

"I think the change in the dynamics will motivate more patients to say, 'Hey, can I have better quality of life while I wait for my [kidney] transplant? Can I have my time back? Am I able to go back to work?'"

FRESENIUS' NXSTAGE ACQUISITION

For years, NxStage had been the main player in the US HHD space with Fresenius' machine *2008H@Home* being the only real US alternative. Fresenius, for its part, is the only US manufacturer with its own clinics and the global leader in dialysis products and services. (See Figure 3.)

NxStage, founded in 1998, won FDA approval for its portable System One dialyzer in 2005 for HHD. In 2014, the company also won FDA approval for home nocturnal dialysis, a real-time approach that creates a dialysis solution using patient's home water supplies and a pre-mixed bag of concentrated substances *(Also see "DIVE INTO DIALYSIS: NxStage Aims To Transform Home Hemodialysis Into $2bn Market" - Medtech Insight, 7 Dec, 2015.)*.

The acquisition looked like a natural fit to Jefferies analyst Raj Denhoy.

No other company but DaVita would have made sense as a buyer, Denhoy said, because access to HHD machinery and training would naturally go through a large service provider.

"At the end of the day [the clinics] do control the path," Denhoy said. "NxStage has only been able to achieve less than 2% market share after trying in this for 10 or 12 years, and I think it just suggests that there are these intractable problems out there and this access issue has always been the biggest one. But now with Fresenius buying it, it sort of opens the road."

He speculated that the need to build less fixed clinic capacity may be an incentive for Fresenius.

"If they can start to lower their cost of in-center care by not building as many facilities, maybe they can start to make that whole equation bend towards where home starts to look more attractive," he said.

If a rising tide lifts all boats, DaVita and other dialysis clinic companies may have to hustle to find a way to offer HHD more widely.

"There are a multitude of players who are heavily invested in legacy solutions, both on the machine side and on the service provision side," Milad said. "For a long time, nobody wanted to make the first move to cannibalize and disrupt a market that was very comfortable for many people. Now that Fresenius has done that, it means others can't afford to be complacent anymore."

QUANTA: USE IT ANYWHERE

Quanta Dialysis Technologies, a private company in Alcester, UK, is betting that a machine versatile enough to be used both in the clinic and at home will open up a bigger HHD market *(Also see "Quanta Brings Oxford Uni Money Man On Board" - Medtech Insight, 22 Sep, 2015.)*.

Its *SC+ dialysis system* is designed to be user-friendly and small while maintaining the high efficacy and dose of typical clinic machines. No pre-mixing of dialysate is required — a step that can take hours and force HHD patients to plan ahead (Image 1).

Dialysate fluids are generated and managed by a single-use disposable cartridge, which its CEO Milad calls the "key breakthrough, enabling a small, user-friendly and powerful device."

With disposable fluid paths, SC+ is also intended to reduce the risk of cross-contamination.

Over the past couple of years, Quanta has piloted SC+ with the UK's National Health Service, where it is generating performance data under a clinical study. Milad expects that the commercial version of SC+ -- which will include wireless uploading of runs sheets and treatment records for physicians -- will debut in the UK in H2 2018 with anticipated FDA clearance in 2019.

Founded in 2008, Quanta's investors include **Air Liquide/ALIAD**, **b-to-v Partners**, **IMI**, **Kuwait LifeSciences Company**, **Stage Capital**, **Seroba Life Sciences**, **Seventure Partners** and **Wellington Partners**. The company has raised over £60m in funds to date, Milad said.

Sized at 45x48x37 cm and weighing 35 kg, SC+ is designed for use either at home or in-center

Photo credit: Quanta Dialysis Technologies

What sets SC+ apart is its compact size and high performance, he noted.

"You have the full flexibility to crank up the device to provide a high-dose treatment like it's done today in the clinic, and then to ease it back and to do it in the more gentle ways that a patient might wish to do in the home," Milad explained.

Milad believes the SC+ is especially suited to a transitional care delivery model, in which patients take weeks or months to gradually learn to self-dialyze in a center before going home with a personal dialysis system.

"We've taken typical dialysis patients, not cherry-picked, and treated them as part of the normal clinical work flow, using their existing prescriptions," Milad said. In post-treatment measures, all patients hit their therapy targets, he added.

In a poster presentation at the EDTA conference in Madrid in June, Quanta showed that in 915 treatments between June 2015 and May 2017, dialysis was adequate and there were no serious adverse events.

OUTSET MEDICAL: IN-CENTER SELF-CARE

Meanwhile, Leslie Trigg, CEO of privately held San Jose, California-based **Outset Medical Inc.** told *Medtech Insight* that her company is currently the only US venture-backed startup focused on hemodialysis machine technology *(Also see "VC Deals Analysis: From Famine To Feast, 2017 Bloats With May Haul" - Medtech Insight, 7 Jun, 2017.)*.

"The lack of innovation to date really baffles the mind when you think about the size, the market opportunity, in terms of the number of episodes of care each year, and the number of patients receiving dialysis," Trigg said.

Outset was originally capitalized in 2010 by **Warburg Pincus** with the aim to rival NxStage in the HHD space, Trigg said. The company closed a series C round in mid-May for $76.5m, which was led by T. Rowe Price Associates, Inc. and included existing investors **Fidelity Management & Research Company**, **Partner Fund Management LP**, **Warburg Pincus**, **Perceptive Advisors** and the **Vertical Group**. To date, the company has raised a total of $190m.

Outset's technology, *Tablo*, which received FDA clearance last November, is heavily automated and designed to be patient-friendly. It is also far less intimidating than the clinic machines, using a touch-screen interface and purifies tap water and makes dialysate in real time.

"Tablo really obviates the need for infrastructure," Trigg explained. "It's like a mini rolling dialysis clinic. You don't need anything else with Tablo, except for an electrical outlet and some source of tap water."

Tablo also incorporates both Wi-Fi and cellular data communication capabilities, uploading vital signs and other data from a session, which "takes the administrative part of dialysis out of the patient's hands," Trigg said. In addition, Tablo is able to receive wireless software updates and patient prescriptions.

"Tablo is currently the only hemodialysis system cleared for two-way data transmission," Trigg added.

Tablo was originally designed for home hemodialysis. But the company is now also aiming at in-hospital and in-center self-care.

With in-center self-care, patients dialyze themselves within a traditional dialysis center as they would at home. Better known in Europe than in the US, the option offers extra support to patients while allowing them more independence and flexibility and keeping labor costs low. In both care settings, Trigg said, Tablo's simplicity, automation, and all-in-one design offers cost advantages for providers.

Tablo has been cleared for use in acute and chronic care settings, and is used in several hospital ICUs and regular floors, according to Trigg, as well as some centers offering it for in-center self-care. Trigg declined to name the health care settings.

Outset isn't forsaking HHD. The company is currently enrolling patients for an IDE study to expand Tablo's label indication for home use.

"We have been very happy with the results so far, and are continuing to move forward," Trigg says. She didn't want to speculate on a timeline for HHD approval, but anticipates a full market release in 2018, initially for in-center and in-hospital indications.

"Patient independence is the future, and our vision is different insofar as we don't believe independence has to mean your only option is home," Trigg said.

REIMBURSEMENT

Reimbursement for HHD remains a challenge in the United States.

Private insurers pay the first 30 months of a patient's dialysis, which is the only time companies like DaVita can make a profit, according to an article that appeared in *NEJM Catalyst*.

Once Medicare kicks in, service providers lose money.

Bundled Medicare payments, that took effect in 2011, support three weekly in-center sessions at $240 each; service providers were paid the same whether the patient is dialyzed in-center or at home. Suddenly, centers had to find cost savings.

With medical justification, doctors can sometimes get a fourth or fifth day of dialysis paid for—most HHD is done five days a week—but Medicare doesn't offer specific HHD incentives other than for training.

"[CMS hasn't] put in place any firm guidelines or rules for paying for more frequent dialysis—it still sort of exists in that grey area," Denhoy said. "I think Medicare also knows that two major providers control 60-70% of the dialysis market in the US, that those entities are very much profit-driven, and if you start creating incentives to do more frequent dialysis and you're paying for more frequent dialysis, your bill is going to go up."

But Milad believes that economics will start to favor HHD.

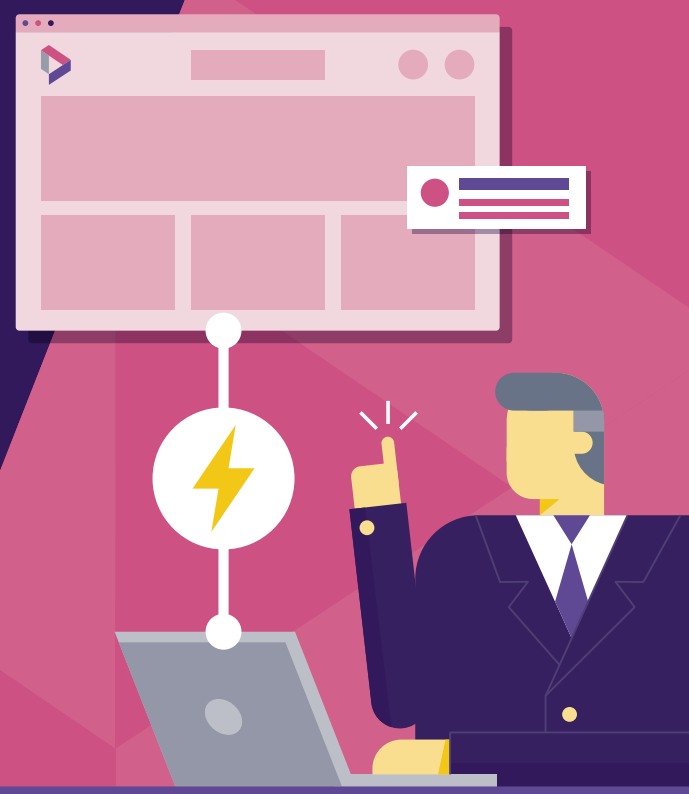
"The provider is going to need to care more about not just what is the cost of an individual therapy, but what is the cost of managing the patient," he said. "To the extent that there are therapeutic options available like HHD, which can simultaneously lower the cost of the therapy while at the same time generating better health outcomes, which will reduce the cost of the total patient burden for managing them, market forces will naturally push providers more towards home therapies —even if the reimbursement per se doesn't change to benefit HHD."

Published online 09/15/17

Pharma intelligence
informa

Less time searching and more time planning your pharma clinical trials?

Yes, please.



The next generation of Citeline revolutionizes Informa's gold standard clinical trial intelligence through an interactive, dynamic new interface, along with technology that allows you to integrate Citeline content directly into your organization's software and workflow tools.

All so you can design and run the next generation of clinical trials to achieve optimal commercial outcomes with less risk and cost.

The result: Enhanced data and insights, delivered to you on your terms.
The outcomes: Better clinical trials for better health outcomes.

Visit **pharmaintelligence.informa.com/nextgeneration** to learn more.

Citeline
Pharma intelligence | informa