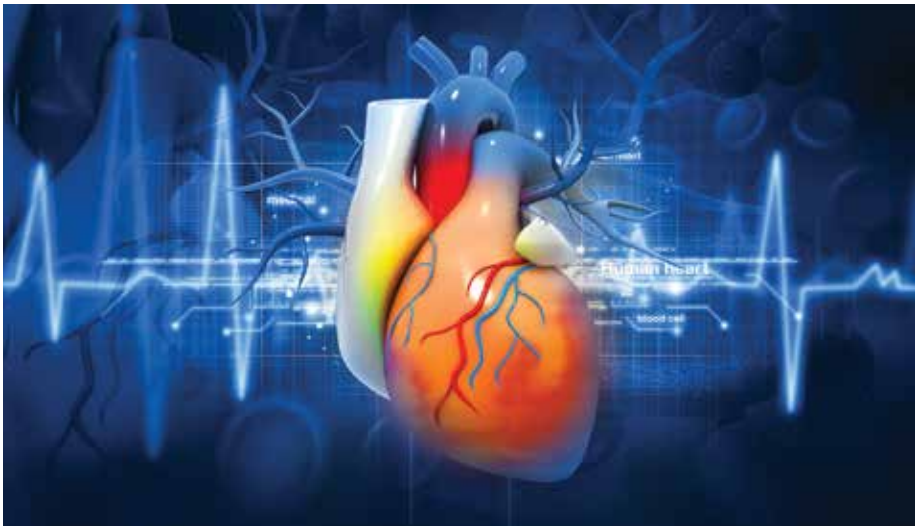
Medtech Insight
Issue 29
medtech.pharmamedtechbi.com
Pharma Intelligence Informa
February 6, 2017



Shutterstock: hywards

Emerging Markets Are Fertile Frontier For CRM Device-Makers

NICK TALAMANTES Nick.c.talamantes@informa.com

The global market for implantable cardiac rhythm management devices, which counts medtech heavyweights such as Medtronic, Boston Scientific, Biotronik – and now Abbott – among its key players, is anticipated to expand from an estimated $10.2bn in 2015 to roughly $13.5bn in total product sales by the year 2021, according to a new *Meddevicetracker* report.

The two major drivers for the surge in CRM products are the rising aging population at risk for developing cardiac rhythm disorders and an overall increase in heart disease, stated the report, entitled "Implantable Cardiac Rhythm Management Device Markets." In addition, technological innovations in the ICD and pacemaker product segments -- such as compatibility with magnetic resonance imaging (MRI) systems, device miniaturization, improved battery longevity, and remote patient-monitoring software – will further expand the numbers of patients eligible for receiving CRM implants. To offset slowing growth in major developed markets, CRM manufacturers are expected to increasingly focus their attention on the emerging markets, which benefit from a rising middle-class and improving modernized health-care infrastructure, according to the MDT report.

A breakdown of individual product segments in the global CRM market shows that in 2015, ICDs accounted for nearly half, or 44.5%, of the total CRM market, followed by implantable pacemakers, which held a 32.7% market share, and cardiac resynchronization therapy systems, which accounted for 22.7% of the market. (See Figure 1.)

REGIONAL INSIGHTS

Geographically, the US is still the biggest CRM market. In 2015, it had 44.9% of the global market share with $4.6bn in sales and is projected to remain the fastest growing market worldwide over the forecast period (2015-2021).

The sophisticated US health-care system that allows patients with potentially severe arrhythmia to be diagnosed quickly and start treatment, as well as the continuing rise of heart disease in the general and aging population, is helping to drive sales of implantable CRM products in this market. However, sales are limited by the fact that it is a saturated market, and average selling prices (ASPs) for all implantable CRM devices are forecast to fall due to intense competition among the few major players.

The five major European markets — France, Germany, Italy, Spain and the UK — together accounted for the second-largest market for implantable CRM device sales in 2015, with an estimated

CONTINUED ON PAGE 19

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

POLICY & REGULATION
Trump's two-for-one regulation plan, p. 8

COMMERCIAL
Verily lands $800m to up Asian presence, p. 17

MARKET ACCESS
CMS jacks bone density scan reimbursement rates, p. 5

Pharma intelligence

informa

Intelligence with a Global Perspective

The Premier Resource In The Life Sciences Industry

- Biomedtracker
- Datamonitor Healthcare
- In Vivo
- Meddevicetracker
- Medtrack
- Medtech Insight
- Pink Sheet
- Pharmaprojects
- RxScorecard
- Scrip
- Sitetrove
- Trialtrove

Pharmaintelligence.informa.com

explore more:

exclusive online content

Unlocking Legalities
http://bit.ly/2krcind
Many device companies still have a lot of work to do to ensure False Claims Act compliance. Read the first article in an occasional series in which *Medtech Insight* talks to attorneys about important legal trends and topics for industry.

MDMA's outlook
http://bit.ly/2kRKCJ9
An interview with Mark Leahey, president and CEO of the Medical Device Manufacturers Association, on the trade group's optimistic outlook for 2017 and the Trump administration.

Avacta eyes first deals for alt antibody tech
http://bit.ly/2kRGSHr
UK protein scaffold specialist Avacta expects to seal its first licensing deal in 2017 for its *Affimer* technology.

Teijin solidifies ortho biz
http://bit.ly/2jD8rPO
Japan's Teijin is adding a family of bioresorbable, osteosynthetic bone-fixation devices to its modest but growing orthopedics portfolio.

Device Week
http://bit.ly/2jVeMH4
Our weekly podcast, where *Medtech Insight* journalists discuss topics they are covering that impact the device and diagnostics sector.

medtech.pharmamedtechbi.com

inside:

Cover / Emerging Markets Are Fertile Frontier For CRM Device-Makers – The global cardiac rhythm management market is set to grow at a compound annual growth rate of 4.8% to about $13.5bn by 2021. This article, based on findings from a Meddevicetracker report, provides an in-depth look at where the growth markets are, the evolving competitive landscape, and discusses the key players and upcoming technological trends that will bolster this market.

EDITORS' PICKS

5 CMS Raises Hospital Reimbursement Rate For Bone Density Scans, But Is It Enough? – Advocacy groups for diagnostic services to test for osteoporosis scored a big win when the US Centers for Medicare and Medicaid Services agreed to raise reimbursement rates for DXA bone density scans in the hospital setting this year rather than cutting the rates as initially proposed. However, there is not such good news for doctors providing in-office DXA scans, as they struggle with continuing declining reimbursement rates that cannot offset the costs of the procedures.

8 Trump's Two-For-One Reg Order Needs Agency Interpretation, Medtech Reg Experts Say – For the most part, industry experts and lobbyists say they still have questions about President Trump's executive order, which requires agencies to rescind two regulations for every one rule that is implemented. With key leadership positions at HHS and FDA still unfilled, some say they are taking a wait-and-see approach before concluding how the order will be interpreted.

POLICY & REGULATION

10 EU's Legal Minefield Is A Notified Body Nightmare – There seems to be no way to tell which way the patient case against TÜV Rheinland tied to safety issues with the infamous PIP breast implants will go. The matter is creating significant uncertainty for notified bodies and the broader medtech legal community.

11 Adoption Of Forthcoming EU Regulations Still On Schedule – It is now looking as if the EU's medtech regulations will be adopted in March and take effect in May, and that the medtech sector will see the very final texts of the forthcoming EU Regulations in the next few weeks.

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

12 Grassley Asks Price To Preserve "Open Payments" Database – Sen. Chuck Grassley urged US Department of Health and Human Services secretary nominee Tom Price to preserve the "Open Payments" database that was established by Grassley's Physician Payment Sunshine Act, even if the Affordable Care Act, by which the Sunshine law was enacted, is repealed.

13 Manufacturers, Physicians Suggest Changes To Ultrasonic Aspirator Labeling Guidance – Comments to a November draft guidance from US FDA request additional clarity and an exemption from correction reporting requirements. A physician group thinks a proposed label warning goes too far.

COMPLIANCE CORNER

14 7 Things To Do – And Not Do – When FDA Inspects Your Facility – Two former US FDA investigators offer do's and don'ts for device firms to follow when their facilities are being inspected. Tips include everything from not boring an investigator during an opening meeting, to making sure quality system fixes are communicated to auditors in a timely fashion.

COMMERCIAL

17 HiberGene's Rapid Group B Strep Test Pregnant With Potential – A year after launching its first product, rapid molecular diagnostics specialist HiberGene now has a trio of infectious diseases tests under its belt. One of the tests, designed to detect Group B *Streptococcus* in pregnant women, is expected to be a major cash generator for the firm once it begins its sales ramp-up.

18 Verily Mulls Asian Acquisitions, Partnerships With $800m Temasek Cash – Verily looks eastward for more health-care opportunities, with a significant $800m investment from Temasek, a Singapore-based investor with established links and experience in Asia.

CMS Raises Hospital Reimbursement Rate For Bone Density Scans – But Is It Enough?

MARION WEBB marion.webb@informa.com

The announcement by the US Centers for Medicare and Medicaid Services on Nov. 14, 2016, to increase reimbursement rates for dual-energy X-ray absorptiometry (DXA) bone scans – considered the gold standard to test for osteoporosis – in the hospital setting to $112.69 after an initially proposed rate cut from the national average of $100.69 to $63.33 may be good news for hospital-based doctors, but it does not address the financial burden faced by private practitioners who perform the majority of these bone density scans, according to the International Society for Clinical Densitometry (ISCD).

Rates of osteoporosis screening via DXA testing have steadily declined since the implementation of the Deficit Reduction Act of 2005, according to a new *Meddevicetracker* report, *Women's Health: Osteoporosis Diagnostic Products*.

Medicare's national average payment for DXA scans in doctor's offices has been steadily dropping over the last decade or so, from $139.46 in 2006 to $40 in 2015, $41.56 in 2016 and $40.78 for 2017, according to ISCD statistics. Only for a brief period (2010 to March 2012) – as a result of congressional intervention – did reimbursement rates for private DXA testing rise to $98, before continuing its downward trend, Donna Fiorentino, ISCD's Legislative Counsel, told *Medtech Insight*. The ISCD represents about 3,000 members including physicians and technologists performing axial DXA scans in both the office and hospital settings, she said.

On the other hand, in the hospital setting, CMS reimbursement rates for DXA testing remained in the $80-range from 2006 through 2013, then rose to $101 in 2014 and $105 in 2015 before declining to $99 in 2016. (See Figure 1).

Fiorentino said she's thrilled that the advocacy efforts by her organization and others, such as the National Osteoporosis Foundation, paid off, but said that serious challenges remain.

Shutterstock: Suttha Buravonk

> "We urged them (CMS) to look at the whole system – office and hospital-based together – and they decided not to impose cuts. It is a huge win for us and we are thrilled that hospital-based physicians are able to provide the service, but it did nothing for the hemorrhaging in the doctor's office"
> *– Donna Fiorentina, Legislative Counsel, International Society for Clinical Densitometry*

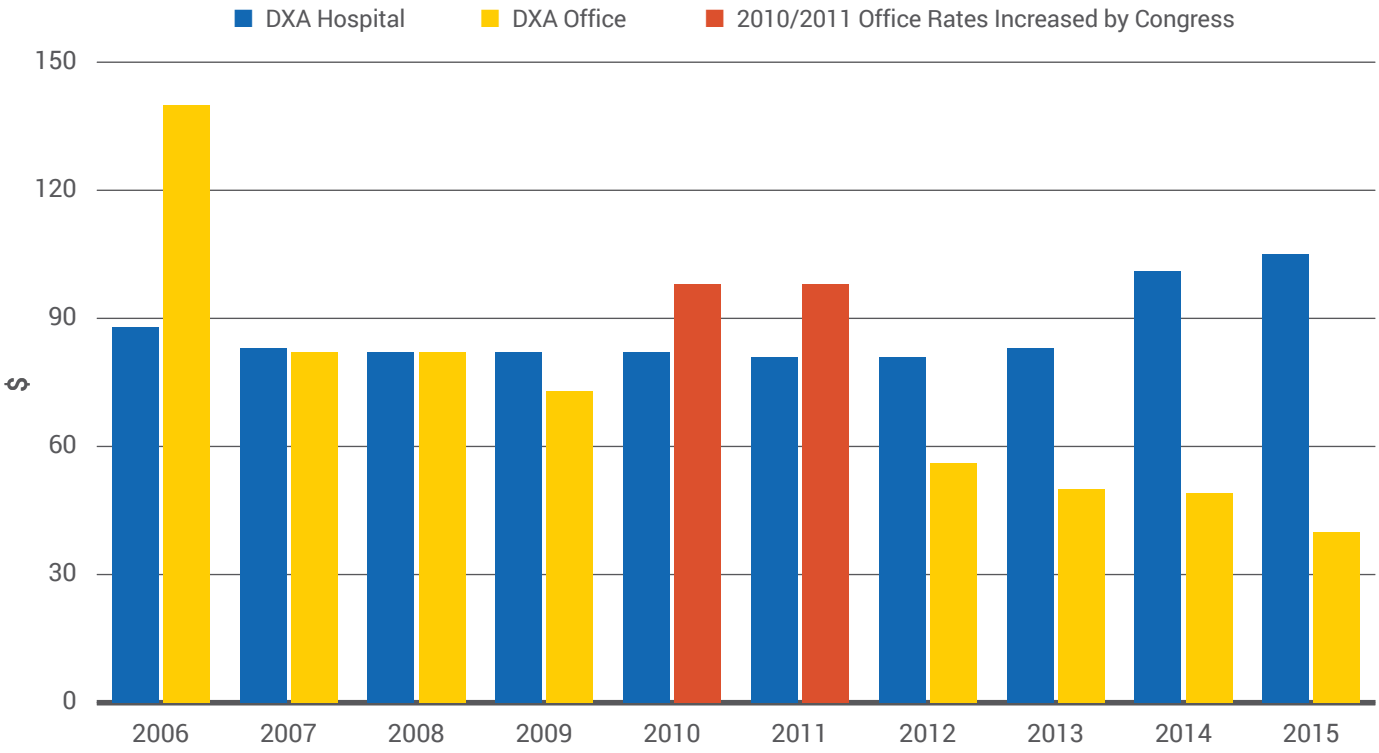
PATIENT ACCESS HURT BY IN-OFFICE REIMBURSEMENT CUTS

About two-thirds of all DXA testing is performed by endocrinologists, gynecologists, rheumatologists and other practitioners in their offices. Many doctors have traditionally incorporated DXA machines into their offices to screen patients who may be treated for other conditions, such as diabetes, obesity or thyroid problems that have been linked to potential bone density issues. The ongoing reimbursement cuts, however have made it increasingly difficult for doctors to offer testing. According to the ISCD, the numbers of DXA office providers declined from 22,355 in 2008 to 15,952 in 2015. (See Figure 2).

With fewer doctors offering DXA screening in their private practices, it has created an access problem for patients, with many hospitals having a backlog of six months and longer to accommodate patients. For many aging patients, who have difficulty getting around, the need to travel to a hospital, then see their provider, is also a major deterrent to getting tested, Fiorentino noted.

FIGURE 1

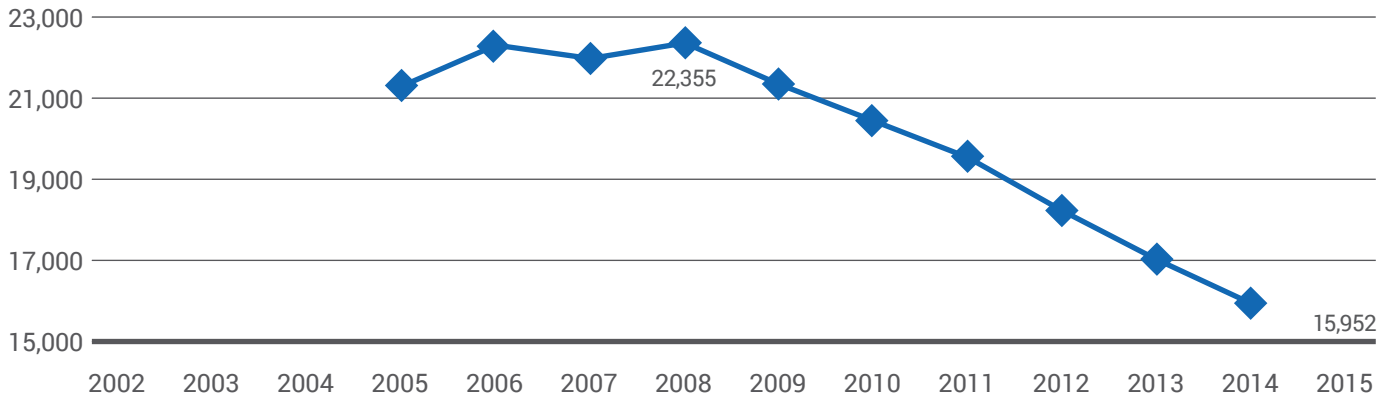
Comparison of Medicare DXA Payment Hospital vs Office



Source: Fiorentino/ISCD

FIGURE 2

No. of DXA Office Providers (2005-2014)



Source: ISCD

"Because Medicare began to cut DXA reimbursement rates in 2007, it was predictable that when you slashed rates to that extent, you'll see a drop in the number of providers and that is exactly what happened," Fiorentino added. "And as reimbursement dropped, you see the percentage of women tested (for osteoporosis) in the Medicare program dropped and those diagnosed with osteoporosis dropped."

The 70% drop in Medicare reimbursement for office-based bone density tests has led to 24% fewer physicians offering bone density testing compared to 2008, resulting in 2.3 million fewer DXA

scans being performed on Medicare-age women. Between 2009 and 2014, osteoporosis diagnosis in Medicare women declined by 18%; women 65 years and older who have a DXA scan have 22% fewer fragility fractures and 35-50% fewer hip fractures than those who don't get scanned.

Statistics by the Bone and Joint Initiative 2016 suggest that after a 30-year downward trend in hip fractures in the US, this decline has now plateaued as a consequence of reduced DXA testing, which, in turn, leads to potential osteoporosis patients not being managed properly.

growing interest in utilizing the technology to assess body composition in the elite fitness, nutrition and weight loss markets," Mazur said.

Claudio Mejia, Lunar Segment Leader for GE Healthcare, which markets the *Lunar iDXA* and *Prodigy DXA* systems to doctors in private offices and hospitals, offers a similar outlook.

"In a broad sense, this segment (bone densitometry) has remained relatively flat over time, which can be greatly attributed to two factors – reimbursement, which accounts for much of the decline – and other dynamics, such as the concern over bisphosphonates used in the treatment of osteoporosis," Mejia told *Medtech Insight*.

> Bone densitometry has remained relatively flat over time due to reimbursement and other concerns like the use of biphosphonates in osteoporosis treatment
> - Claudio Mejia, GE Healthcare

MANUFACTURERS SEE INCREASED SCREENING BEYOND BONE HEALTH

Jane Mazur, a spokeswoman for Hologic Inc., which markets the *Horizon DXA* system in the US under its skeletal health division, told *Medtech Insight* that the drop in Medicare reimbursement rates for DXA scans has led to an "alarming change in the trend line on hip fracture."

"Ultimately, lower reimbursement has resulted in fewer providers and less DXA scans being performed," Mazur said. "Unsurprisingly, this has resulted in smaller numbers of women being diagnosed and treated for osteoporosis or osteopenia, which has led to an increase in fractures."

At the same time, she said that even through the downturn in reimbursement, Hologic hasn't seen declining DXA sales and even introduced its newest-generation Horizon DXA system to private doctors and in hospitals in the second quarter of fiscal year 2014.

She noted that other factors, beyond reimbursement, impact DXA sales.

"For example, Hologic is starting to see

He also sees the technology increasingly being used "beyond bone health."

"Other things you can test for related to body composition – weight management, diabetes, obesity and lean muscle mass and sarcopenia – are getting increased visibility out there," he said. "DXA can also be used for healthy populations where you can do body composition-type screening of healthy populations for athletic performance."

According to the *Meddevicetracker* report, in 2015, Hologic was the second-leading competitor in the US with a market share of 39% and about $39.3m in densitometer products sales behind market leader GE Healthcare, which held a 47% market share and posted about $47.4m in product sales.

Still, everyone agreed that historically when reimbursement rates for DXA testing are higher, it correlates into more doctors prescribing and conducting bone density tests, which translates into more high-risk fracture patients being diagnosed and treated earlier.

SLIGHT INCREASE LITTLE GAIN

According to the *Meddevicetracker* report, osteoporosis was among the 10 costliest chronic conditions covered by Medicare in 2010. Fractures from osteoporosis and low bone mass cost the US health-care system about $20bn annually and will reach $25bn by 2025 as the elderly population nearly doubles.

Fiorentino doesn't expect the slight increase in DXA reimbursement for hospital-based physicians to lead to a significant rise in DXA testing.

"A $10 increase isn't a huge increase and won't lead hospital-based DXA to explode," she said.

She said more needs to be done to keep DXA machines in the hands of private practitioners. The ISCD is part of the Fracture Prevention Coalition, which includes the National Bone Health Alliance, National Osteoporosis Foundation and the American Society for Bone and Mineral Research, among other organizations advocating to address the effects of DXA reimbursement cuts on patient access to care, she added.

"The trend of loss of physicians isn't leveling off," Fiorentino noted. "We lost over 1,000 physicians in 2014 alone. The loss of expertise in this area just cannot be understated. It's horrible for patient care."

Mazur agreed that office-based DXA screening for patients is critical.

"Making this critical test more easily accessible to patients will help to increase compliance and ensure that as many patients as possible are screened," she told *Medtech Insight*, adding that, "If we want to reverse the startling trend of increasing hip fractures, office-based reimbursement rates need to be addressed."

Fiorentino said higher reimbursement rates for DXA office providers would help turn things around, but it would take years to achieve the prevention levels from a decade ago.

"The progress we made in osteoporosis care has just been totally undermined," she said. "It will take awhile for that progress to reverse and more physicians to become involved and patients to get back into the system."

Published on 01/29/17

Trump's Two-For-One Reg Order Needs Agency Interpretation, Medtech Reg Experts Say

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

Under a new executive order issued by President Donald Trump, all executive branch agencies would be required to rescind two regulations for every regulation they implement. Life-science regulatory experts say the language requires interpretation from individual agencies to understand its full impact. Lobby groups say they will keep a close eye on the measure, while key hospital group is praising the move.

Since taking office Jan. 20, the new president has signed a string of executive orders, including a hiring freeze on executive branch workers and an immigration ban from targeted countries. On Jan. 30, he continued the trend by signing an order that would emulate policies in countries such as the UK and Canada to reduce regulations.

"Unless prohibited by law, whenever an executive department or agency ... publicly proposes for notice and comment or otherwise promulgates a new regulation, it shall identify at least two existing regulations to be repealed," states the order.

The president has also ordered all agency heads to make sure that any new regulations that are put into place in the current fiscal year do not increase costs, unless required by law or consented by the Office of Management and Budget.

The order further states that directors of departments must update the agencies they direct as part of the president's budget process on how much incremental cost they are allowed to take on during the following fiscal year.

"No regulations exceeding the agency's total incremental cost allowance will be permitted in that fiscal year, unless required by law or approved in writing by the director," the order states. "The total incremental cost allowance may allow an increase or require a reduction in total regulatory cost."

GUIDANCE DOCS INCLUDED?

According to the order, a regulation is defined, based on the Administrative Procedure Act, as a "statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy or to describe the procedure or practice requirements of an agency."

The document exempts regulations that apply to the military, national security and issues of foreign affairs, and also those that deal with agency organization, management or personnel, as well as any other categories of regulations exempted by department directors.

James Boiani, an attorney with the law firm Epstein Becker Green who specializes in regulations for clinical diagnostics, says the order is written too broadly to provide a detailed interpretation in isolation. Each agency will need to interpret the language to determine the impact on regulators such as FDA and the industries they oversee, he told *Medtech Insight*. The fact that a permanent Health and Human Services Secretary has yet to be confirmed and a permanent FDA commissioner has yet to be nominated is likely to further delay full interpretation of the orders, he suggested.

Shutterstock: Gajus

"I'm just wondering if, sans granularity, this will accomplish what it is intended to accomplish or will simply add more time to figuring out how to navigate around new bureaucratic rules that spin out of the EO," attorney James Boiani says.

"Regarding the definition of a regulation, is it a chapter/part in the CFR, or a section, sub-section, subparagraph, etc. that makes a regulation?" asks Boiani. "Will agencies ultimately get around this by condensing regulations?"

Bradley Thompson, a colleague of Boiani's and a device regulatory expert, says, based on the definition set forth by the order, he does not think a guidance document will necessarily be considered a regulation if the document's subject is "truly" addressed through the guidance.

"In the two-for-one document issued today, they do not say that regulation includes guidance documents," Thompson said. "[It] makes me wonder if that's intentional. I could see them

freezing all pronouncements, whether regulations or guidance documents. I could see them separately imposing these limits on new regulations because new regulations include new requirements, where guidance documents clarify existing requirements and thus there is not the need for the two-for-one limit."

Thompson also notes with interest that the order not only addresses the number of regulations but also the costs associated with them.

"The executive order seems intent to stop the growing cost of compliance with regulations. So guidance could be relevant if it reflects the true costs of existing regulations that form the legal authority for the guidance," he said. "In other words, a guidance that increases the cost burden on industry is likely to face OMB objection because of that cost impact, regardless of the two-for-one deal."

Boiani adds that there are many ways of scoring costs that could let agencies "dance around" the cost cap.

"I'm just wondering if, sans granularity, this will accomplish what it is intended to accomplish or will simply add more time to figuring out how to navigate around new bureaucratic rules that spin out of the EO," he added.

DOUBLE-EDGED SWORD?

The executive order "is a sea change with much greater regard for the cost of regulation," said Jeffrey Shapiro, an attorney with Hyman, Phelps and McNamara and medtech regulatory expert, in an interview.

But he says the order could be a double-edged sword that, on the one hand, could help reduce regulatory burden, but also might discourage guidance sorely needed by industry.

Some medtech industry advocacy groups are worried about that issue, while others say they are taking a wait-and-see approach.

"Encouraging innovation in medicine requires thoughtful consideration of how regulatory policies can enhance our ability to deliver the right therapy to the right patient at the right time," said Edward Abrahams, president of the Personalized Medicine Coalition. "Requiring regulatory agencies to base their decisions on an arbitrary formula could discourage innovation and therefore negatively impact the health of the nation."

Scott Whitaker, president of AdvaMed, says his group is reviewing the order and looks forward to hashing out the details with the administration.

"We have long maintained that any regulation needs to benefit patients and foster innovation, and the medical technology industry has developed a strong working relationship with key agencies such as FDA and CMS in support of those principles," he added.

Rick Pollack, president of the American Hospital Association, meanwhile, says he's encouraged by the order because he thinks it will reduce red tape.

"The regulatory burden that is imposed on hospitals and health systems is substantial and unsustainable, and has grown in recent years," he said. "Reducing the administrative complexity of health care would allow providers to spend more time on patients, not paperwork."

He noted that over the past year the federal government has added more than 23,000 pages to existing regulations that affect hospitals and the health-care system.

TAKING CUES FROM OTHER NATIONS

Thompson, from Epstein Becker Green, is also general counsel for the Clinical Decision Support coalition, an industry group that engages the government on health-software regulations. He says there are one or two rules that the digital health industry needs, including one to down-classify certain digital health accessory products and clinical decision support software. The rules could reduce the cost of compliance for industry and, he says, FDA, which might allow the agency to increase cost in other areas.

"The regulatory burden that is imposed on hospitals and health systems is substantial and unsustainable, and has grown in recent years," says Rick Pollack, president of the American Hospital Association.

"Overall, I expect FDA to use guidance now more than ever. So long as they can defend the use of guidance instead of rulemaking, the use of guidance will help the agency potentially avoid the limits imposed by the executive order," he said. "But if industry can show that new guidance effectively raises the cost of compliance, industry may be able to push back on even new guidance."

The idea of a two-for-one system to streamline regulations isn't new. Similar approaches have been applied, for instance, in Canada, which adopted a one-for-one rule in 2012. However, the order from Trump may come more caveats, observers suggest.

"Overall, the spirit and intent of the executive order seems designed at a high level to reduce the cost of compliance, and ultimately that has to help the digital health industry as well as the medical device industry more broadly," said Thompson. "FDA retains the ability to proceed with regulations that are required by Congress. This only affects discretionary regulations that FDA might decide to pursue without being specifically directed to by Congress."

Thompson says the big take away for FDA may be that it can continue to fulfill its mission but it will need to be more sensitive to costs. The order will also push the agency to look for outdated regulations that may be imposing unnecessary costs to offset new costs, he said.

Published online 01/30/17

EU's Legal Minefield Is A Notified Body Nightmare

AMANDA MAXWELL amanda.maxwell@informa.com

The outcome of the case of the PIP breast implant recipients against notified body TÜV Rheinland LGA Products is not a sure thing.

Part of the reason for this is because of the specifics of the court system in France.

Another major question for the case is the extent to which judges are prepared to accept the complexity of the medtech regulatory system, specifically the fact that companies in many cases have had to demonstrate a compliant quality system rather than compliant products to a notified body. In other words, will judges accept that there have been options in the system which did not involve the actual testing of the products?

A third issue is that the judgments that are made will not apply throughout different countries. Even when a ruling is given by the European Court of Justice – and we do not know yet which way that will go – it will answer very specific questions on the regulations and not decide the facts of the case. This suggests there may never be any conclusive, single EU-wide answer to the liability question for notified bodies.

All of that means TÜV Rheinland, the notified body that audited the quality system of Poly Implant Prosthèse, seems to be in for a bumpy ride. And not just TÜV, but all notified bodies in the medtech sector are going to be anxiously watching developments and assessing how best to protect themselves in the future.

CHAIN OF EVENTS

Turning first to the court system in France and the confusing chain of events that have taken place there.

> There is no binding precedent in France; any court can effectively rule according to its own interpretation of the facts, attorney Cécile Derycke, representing TÜV Rheinland in the case, tells *Medtech Insight*.

The Court of Toulon has just ruled for the second time against TÜV Rheinland. It made essentially the same ruling in favor of PIP breast implant plaintiffs and distributors of the implants as in the first case in 2013. *(Also see "New PIP Court Ruling Sends Further Shockwaves Through EU Medtech Sector" - Medtech Insight, 23 Jan, 2017.)* Yet this is despite the fact that the Aix-en-Provence Court had overturned this ruling in 2015 after TÜV Rheinland had taken its appeal there.

Cécile Derycke, the Hogan Lovells litigation partner representing TÜV Rheinland in the case, explained to *Medtech Insight* that this has occurred because there is no binding precedent in France; any court can effectively rule according to its own interpretation of the facts.

Indeed, the Toulon court, having first ruled in favor of the 1,700 women implanted with the device in 2013, has effectively become a magnet, for anyone else wishing to benefit from the same ruling.

The Toulon Court is the only court to have ruled against TÜV Rheinland's notified body, Derycke explained. All of the other civil and criminal courts in France and Germany have rejected the claims, she said (although one has referred questions to the European Court of Justice). Not only the Aix-en-Provence court of appeal (in 2015), but also the Civil Court in Paris (in 2014) has rejected claims brought against TÜV Rheinland. There have been multiple cases in Germany that have found in favor of TÜV Rheinland, one on appeal, she said.

A similar case is currently pending before the French Supreme Court. An appeal was made by some of the plaintiffs to the Supreme Court after the 2015 overturning at Aix-en-Provence.

STRATEGY IN TIMING OF LATEST CASE

The counsel acting on behalf of TÜV Rheinland had asked the Toulon court to await a ruling from the Supreme Court.

It felt this was particularly important given TÜV Rheinland had already borne the brunt of the financial costs of having a ruling overturned after having been ordered to pay compensation. Indeed, although the German notified body had requested money back from the recipients in the first Toulon case, only a small minority offered to pay. Even monies that had been kept by the Toulon court as part of the legislative process – some €700,000 – which were released to the plaintiffs when the court of appeals overruled the Toulon court, were not used to reimburse TÜV Rheinland, Derycke explained.

TÜV Rheinland will now appeal the merits and enforcement of this lat-

The opinion of the advocate general at the European Court of Justice, made as a preliminary opinion before the full opinion of the court, was made public on Sept. 15, 2016. It reflects the complexity of this legal issue and raises a host of questions that will leave industry guessing not only about the fate of the German notified body, but what the liability position is for notified bodies, in general, with respect to patients for all risk classes of medical devices.

est Toulon case and ask the Aix-en-Provence first presiding judge of the court of appeals for a stay of execution on paying the €60m compensation to the plaintiffs ordered in the latest Toulon case until the appeal has been decided.

'RIGHT OR WRONG' IS NOT THE QUESTION

The discussion on enforcement is not about whether one is right or wrong according to merit, Derycke said. At the very least, one must prove that the enforcement of the liability ruling (the Toulon judgment) would have obviously excessive consequences. This brings to mind the risk of rising notified body insurances and the willingness of notified bodies to continue operating in an increasingly strict, and financially and legally, precarious environment.

The Toulon Court is saying that when one is a notified body, one is guaranteeing the safety of all the products put on the market by the manufacturer. Even though the notified body is not based at the facility and audits only from time to time – and even though TÜV Rheinland was certifying the quality system and the design dossier, and not examining the products – the Toulon Court found it to be liable.

WILL THE ECJ RULING COUNT?

Derycke says she has heard that the ECJ ruling could be ready in mid-February. But it is hard to tell what its impact will be. The ECJ will respond to fairly abstract questions. So, whatever the outcome, it is by no means clear what it will mean for this and future cases. Moreover, in practice, the courts in member states bear ECJ rulings in mind, but ultimately make their own decisions.

Overall, medtech notified bodies remain in limbo at this time, with the adoption of new medical device and IVD regulations coming soon, when they could do with more clarity.

Published online 01/25/17

Adoption Of Forthcoming EU Regulations Still On Schedule

AMANDA MAXWELL amanda.maxwell@informa.com

The final texts of the EU's Medical Devices and IVD Regulations are due to be published "in the coming weeks," *Medtech Insight* has learned.

They will be made publicly available ahead of the March 7 scheduled date for adoption by the Council of the European Union's General Affairs Council.

Once the Council has adopted them, the European Parliament will hold a plenary vote – planned for April – to agree on the regulations as adopted by the Council.

After the Parliament vote, which is expected to be a formality, the regulations will be considered adopted by both regulators and, as long as there has been agreement, the texts will be formally published in the Official Journal of the European Union (OJEU) and enter into force on the 20th day after publication. This will most likely happen by the end of May.

LAWYER-LINGUISTS FINE-TUNE

The texts are currently being reviewed by the European Commission's lawyer-linguists who are expected to finalize their work by the end of this week.

The work of these lawyer-linguists is to draft a legally sound and comprehensible text on the basis of the political agreement reached by the Council of the European Union, the European Parliament and the European Commission in June 2016. It is not to amend the political agreement that was reached.

However, it seems likely that there will at least be some clarification of points that have caused confusion, *Medtech Insight* understands, including the status of products and certificates during the transitional period. The transitional period extends from the time the regulations enter into force until they are fully applied – set to be three years for the Medical Devices Regulation and five years in the case of the IVD Regulation.

Published online 01/24/17

Grassley Asks Price To Preserve 'Open Payments' Database

SUE DARCEY sue.darcey@informa.com

Sen. Chuck Grassley, R-Iowa, used the Senate Finance Committee confirmation hearing for Rep. Tom Price, R-Ga., to serve as the US Department of Health and Human Services secretary to seek a commitment by the Trump administration to keep the "Open Payments" website open, even if the Affordable Care Act that gave the website life is repealed. The panel is expected to vote on his confirmation soon, although no date has been set.

The Open Payments website is a product of the Physician Payment Sunshine Act first introduced by Grassley in 2007, and attached to the ACA before its passage in 2010. It requires device and drug manufacturers to publicly report their transactions of value (royalties, consulting fees, stock shares, etc.) to doctors and teaching hospitals. *(Also see "Company Payments To Teaching Hospitals Hard To Distinguish In Open Payments" - Medtech Insight, 2 Aug, 2016.)* The website and its associated databases are the public-facing vehicle for the reports, and critical for patients who would like to research whether their physicians took payments from the companies making the devices and drugs they prescribe for patients' use. Reporting payments to the database, however, has been described by some device firms as inefficient and burdensome. *(Also see "CMS Says 'Open Payments' Data Easier To Use, But Some See Reporting Inefficiencies" - Medtech Insight, 30 Jun, 2016.)*

"I got legislation passed a few years ago, called the 'Physicians Payment Sunshine Act,' and the only reason I bring this up is because it took Sen. Wyden [Sen. Ron Wyden, D-Ore., ranking member of the Senate Finance Committee] and me last December working hard to stop the House of Representatives from cutting that legislation [as part of] Cures Act passage," Grassley told Price.

"[The law] doesn't prohibit anything, it only has reporting requirements," Grassley explained, adding, "It brings out principles of transparency, which lead to accountability."

"So I'd like to know, if you're confirmed, would you help me make sure, as Secretary of Health and Human Services, that this transparency law is not weakened?"

Price, an orthopedic surgeon, answered that the law was "important work," and significant because "it gives patients a chance to know what is going on with their doctors and the payments they receive," but he gave no indication whether he would salvage the website during the new Republican administration's planned ACA repeal-and-replace process.

In late November, Grassley and Wyden successfully opposed a provision in Cures that would have weakened Open Payments, by making study results on a medical technology or drug published in medical journals that are passed on to physicians by companies as "non-reportable" items.

Grassley publicly stated he would oppose the Cures bill once it reached the Senate floor if that provision had remained intact, remarking: "Watering down sunshine provisions is counterproductive and goes against the trend in health care to have more transparency, not less." *(Also see "Senate Poised To Vote On Cures Bill; Headed To Likely Enactment This Term" - Medtech Insight, 1 Dec, 2016.)*

Photo credit: Sue Darcey

All eyes are on HHS Secretary nominee Tom Price, R-Ga., as he testifies at his Senate Finance confirmation hearing

> While Price acknowledged that the sunshine law was "important work," he made no promises about retaining it during the Trump administration's planned ACA repeal-and-replace process.

Grassley also told Price that the transparency law – which had been incorporated into ACA during its approval in 2010 – took several years to be implemented effectively, and that the Open Payments website it requires has only been in operation for two-and-a-half years.

In all of 2014, for example, the website reported that more than 11.84 million financial transactions from device and drug firms worth more than $7.48bn were made to physicians, including individual payments in the orthopedic space of $3.75m in royalties to a Denver physician, and $2.83m in royalties to an Arlington, Va. orthopedist. *(Also see "CMS Releases 2014 Open Payments Data; Industry Payments To Docs Top $6.49 Billion" - Medtech Insight, 1 Jul, 2015.)*

Grassley also warned during his statements to Price: "If you [or House legislators] strip this legislation, well, then they should

know, Sen. Blumenthal [Sen. Richard Blumenthal, D-Conn.] and I are thinking about expanding it to include nurse practitioners and physicians assistants."

PRICE WANTS DIFFERENT ROLE FOR CMS INNOVATION CENTER

The panelists also questioned Price closely about expansion of Medicaid, his stock purchases that appear to present a conflict of interest, and his intentions for the Center for Medicare and Medicaid Innovation during the Jan. 24 confirmation hearing.

Regarding the CMMI, for example, Sen. Mark Warner, D-Va., asked Price, "Do you support CMMI comprehensive quality-of-care demonstration programs that have the potential to reduce Medicare spending?"

One demonstration program in the orthopedic space that CMMI initiated last spring is the comprehensive care for joint replacement (CJR) payment model. Price introduced a bill in March 2016 known as the "The HIP Act" that would delay or suspend CJR. *(Also see "HHS Nominee Price's Stock Picks To Surface At Confirmation Hearings" - Medtech Insight, 17 Jan, 2017.)*

Price responded: "We must be sure we deliver care in a cost-effective manner." He said the demo programs should emphasize quality of care, and that for some patient populations, "bundled payments" like those in the CJR model "make a lot of sense."

However, in answer to further probing by Warner on the topic, the congressman said he would not necessarily expand CMMI's comprehensive care demonstration programs.

"What I would do, is allow for all types of innovation, not just what these programs emphasize," Price stated, adding that in some cases, "rationing of care" may not improve quality of health care.

Published online 01/2517

Manufacturers, Physicians Suggest Changes To Ultrasonic Aspirator Labeling Guidance

ELIZABETH ORR elizabeth.orr@informa.com

FDA shouldn't require manufacturers adding a newly required warning label to ultrasonic surgical aspirator devices to submit a correction report, companies told FDA in written comments to recent draft guidance.

The draft guidance document, issued Nov. 10, 2016, applies to surgical tools that use ultrasonic energy to break apart and disperse hard and soft tissue. *(Also see "US FDA: Ultrasonic Tools Shouldn't Be Used For Uterine Surgery" - Medtech Insight, 14 Nov, 2016.)* An oscillating tip delivers ultrasonic energy that allows the device to vacuum tissue fragments into the device's inner chamber. The aspirators are frequently used in plastic surgery, neurosurgery, orthopedic surgery, and other operations, and to remove cancerous tissue as a supplement to chemotherapy or radiation treatment.

However, the design of the devices may allow some tissue to escape, which could pose a risk if the device is used off-label to treat uterine fibroids. The FDA draft guidance recommends that packaging for the aspirators include a warning label against using the devices to treat uterine fibroids.

FDA received four comments on the draft before the comment period closed on Jan. 9. Two of the comments are from device-makers, one from a physician group, and one from an individual.

Integra LifeSciences said FDA shouldn't require manufacturers who add the fibroid warning to file a correction report. The company also suggested that companies be allowed to provide the updated labeling to consumers by posting it online, with paper copies available upon request.

The Plainsboro, NJ-based company also asked FDA to amend the guidance to clarify whether the recommendations would apply to products with both general and specific indications for use within general, laparoscopic and gynecologic surgery. As written, the draft seems to only apply to products with general indications for use in those three fields. "We believe it is FDA's intent to recommend the labeling statement for devices that include specific indications for use within those surgical realms, as well," Integra writes, suggesting revised wording that would clarify the point.

Meanwhile, Medtronic PLC said the draft should be edited to clarify the difference between ultrasonic dissectors and ultrasonic aspirators. The guidance wouldn't apply to dissectors.

"Using the common name for ultrasonic dissectors is a more precise way to explain the differences in the device categories. Aspiration, per se, is not the source of the risk being addressed by this guidance document," the company said.

The American College of Obstetricians and Gynecologists noted that, while ultrasonic aspirators are not normally used for myectomies or hysterectomies, minimally invasive approaches are often safest for uterine surgery. Therefore, the doctors said FDA should emphasize a benefit-risk approach and informed consent, rather than the rigid contraindication in the proposed warning label.

The labeling change would take effect 120 days after the release of final guidance.

Published online 01/30/17

COMPLIANCE CORNER:

7 Things To Do – And Not Do – When FDA Inspects Your Facility

SHAWN M. SCHMITT shawn.schmitt@informa.com

Device manufacturers that bore US FDA investigators, fail to communicate properly or don't train top management on agency inspections are on a path to enforcement trouble, two former agency auditors warn.

That advice – along with four other inspection do's and don'ts – came during a panel discussion at the 11th annual FDA Inspections Summit in Bethesda, Md. The experts were Bryan Coleman, senior director of pharmaceutical and device consulting services at EAS Consulting Group, and a former FDA investigator/consumer safety officer; and Ricki Chase, compliance practice director at Lachman Consultants, and a former director of FDA's Investigations Branch.

Comments were edited by *Medtech Insight* for clarity.

Shutterstock: Roman Motizov

"Don't play that game of, 'No, you can't see the CEO.' If I can't see your CEO and I know he's onsite, I want to know what you're hiding. That's what I want to know," former FDAer Ricki Chase says.

DON'T BORE INVESTIGATORS AT OPENING MEETINGS

Bryan Coleman: "A device firm's opening meeting presentation is a great tool if it's done appropriately. That's because in the first 15 or 20 minutes, once everybody got into the room and the inspection was set to begin, I was able to collect a lot of information that I was obligated to collect and report on. So, things like the square footage of the manufacturing facilities, the number of personnel that were onsite, the normal business operating hours and days, who the head of the company was, and how that site linked to that accountable management.

"But what I didn't appreciate was the 70-slide presentation from device firms that bored me into submission. I felt like I was wasting my time and that the firms were trying to delay me from getting inside the facility.

"But again, if you put the meeting together correctly, succinctly and accurately, it's a very good tool to provide information for the FDA as well as for yourselves, particularly if you're the site manager and you happen to be offsite when the FDA shows up – somebody else can step into that and give a solid presentation that's factual and accurate, and has already been pre-worked out. You don't have to guess. You don't have to give inaccurate statements in your quest to answer questions."

Ricki Chase: "I agree, as long as the meetings are done well, and they're short, and they provide the pertinent information. This is not the time to get up and tell the FDA your glory story about how wonderful you are, and how you're saving the world, and how children in some foreign country are going to die if the agency takes your product off the market. Not the time. Not the place.

"But if the meeting has those kind of top-level documents, the floor plans, stuff like that, it's very, very helpful. But don't be surprised if an FDA investigator says, 'I don't want to hear it.' If the investigator doesn't want to hear a presentation and you were planning on giving one, then at least give them a handout of the slides because they're going to want to put that in the report as an exhibit. So, just use an opening meeting wisely."

DO ASK INVESTIGATORS WHY THEY'RE THERE

Coleman: "If for some reason it slips the investigator's mind and he or she doesn't tell you why they're there – some of them tend to be somewhat closed-mouth; they don't like to divulge even though we generally expect that they

will tell you their purpose and scope – then ask them.

"When I was an investigator, I walked into a facility, and because I was probably distracted, I didn't explain that I was there for a pre-approval inspection. So, the site was preparing for a general surveillance audit right before my eyes. It wasn't until about two or three hours into the inspection that I noticed they kept pushing things to me that I wasn't prepared to look at and were not the things I would focus on in the first two or three days. That's when I realized I didn't tell the firm that I was here for a pre-approval inspection.

"Telling the firm that changed how they reacted and responded, and actually improved the efficiency at which the employees got me documents and the people answered my questions. So, it is worth asking those clarifying questions."

DO 'TRAIN UP'

Chase: "When the investigator arrives, he or she is going to say, 'Who is the most responsible individual at this location for this facility?' And the firm is going to say, 'Well, that's CEO John.' The investigator will then say, 'OK, I need to see CEO John because I need to issue CEO John the FDA-482 [notice of inspection].' And the firm might say, 'Well, no, no, no, you're not going to see CEO John because I've been delegated as the management rep, and I'm head of quality and I'm going to take your 482.' Now you're just getting into an unnecessary disagreement. Don't do that. Because now it looks like your CEO is trying to escape culpability, so the CEO can later say, 'I didn't get the 482. I'm not responsible.'

"Sometimes manufacturers don't train up. You've got the head of quality, you've got the head of ops, you've got all these people who day-to-day actually run the company, and then you've got the businessman up there, you've got your CEO sitting up there, and he doesn't know the first thing about accepting an FDA-482 and getting through an FDA inspection. And it's true; I've seen it happen.

"So, don't forget to train up. Your corporate people, your heads of your businesses, need to know and they need to be trained as well, if for no other reason than to expect to come into the room and receive the piece of paper, and smile and shake hands, and then they can run away. But the investigator will ask, so don't play that game of, 'No, you can't see the CEO.' If I can't see your CEO and I know he's onsite, I want to know what you're hiding. That's what I would want to know."

"A close-out meeting isn't an opportunity to put your heel on an investigator's throat and beat your ideas into them before they leave," consultant Bryan Coleman says.

DON'T STIFLE CONVERSATION

Chase: "Try to be open to having conversation at any time about anything with the investigator, because good communication is what's going to make things end well for you. So, try not to stifle the conversation. Investigators are taught to communicate. They're taught that they are supposed to have a daily debrief with firms. There's no reason not to have one.

"Now, that doesn't mean they're going to lay all their cards on the table, because frequently the investigator's still trying to figure everything out. They might say, 'I don't really want to pull the trigger on that with you yet because I'm not sure that it's an issue.' They don't want to be premature and set off alarms. They might think on it, and come back the next morning and say, 'I had time to really think about this last night and look over these documents while I was sitting in my hotel room, and I have some questions about this.'

"The other purpose of a daily debrief is this: You should ask the investigator, 'Is there anything that you didn't get today that you were expecting to get? Did we miss anything? Is there anything we can prepare for you this evening that would be available for you in the morning that would help facilitate the inspection?' And you should have people prepared to stay over and do those things because you want to get the investigators out of your facility as fast as possible. Making sure you're closing the loop and trying to work ahead will help you do that. And the investigators will appreciate that, too, because that means they won't be sitting around waiting."

DO COMMUNICATE FIXES IN A TIMELY MANNER

Chase: "Consider this example: An investigator is walking through your facility and notices that you have a bunch of trash in a corner. The next morning you say to the investigator, 'I want you to know that we got housekeeping out here and we got all that cleaned up. Do you want to take a look at that and you can see that we addressed the issue?'

"Most of the time the investigator is going to respond, 'You addressed the issue. That's great.' And the investigator will make a note in his or her journal, 'The firm corrected that,' if the firm corrected it onsite during the course of the inspection.

"So, there are things that you can correct that are small things that are very easy. They're visual. You can just look at them and say, 'Yeah, I did it. I put the handwashing sign up in the gowning area.' But don't wait until the end of the inspection to say that, because if you have an FDA-483 [inspection observation form] and you're going through the observations, and you're saying, 'Well, no, look, we did this, we did this, we did this,' now the investigator is feeling very overwhelmed because now not only do they have to talk to you about everything on the 483, but now you're wanting them to look at your corrective action that you started in the process. The investigator doesn't want to look at it then.

"So, if you work on something overnight, just say, 'Hey, we opened a CAPA [corrective and preventive action] on that. We'd like to show you that we did that. This is kind of the basis of where we're thinking about going. Could we leave that for you?' That saves having to have that conversation at the inspectional close-

out, and again, it shows that you're being proactive. You didn't wait till the last minute. And it also gives the investigator an opportunity to give you feedback on it, which can be invaluable."

DON'T WASTE TIME ANNOTATING THE FDA-483

Chase: "I think there's very little value to annotating an FDA-483 if every notation is 'under consideration.' I should hope it's under consideration. If that's all you have to say, is that it's under consideration, then just don't say anything at all because it doesn't make any sense.

"I know that industry pushed for device 483s to be annotated. But it completely lacks value. Nobody at the agency cares what you say on there. They don't. You could say, 'I'm going to correct that in the next five days.' But nobody cares, OK?

"I'm just keeping it real. Annotate or don't annotate, but if you're going to annotate, at least be creative about it, because it's not value-added. However, your 15-day response to a 483 – there you have some value added. So, I would recommend simply saying to the investigator, 'I don't need to annotate. Please just make a note that we will respond to the FDA within 15 business days. That you can take to the bank. Please put that in the EIR [Establishment Inspection Report].' And then spend your time and energy around that.

"Because if you commit to doing something within the next five days and you don't do it, then you're going to spend a lot of time talking about why you didn't do what you said you were going to do. So, don't create more work for yourself and more opportunity to fail. It's not value-added."

DO BE CORDIAL AT THE CLOSE-OUT MEETING

Coleman: "Generally, the most responsible person at the site should be at the close-out meeting to receive the feedback and/or the FDA-483. Your key quality heads and business unit leaders, the operations management team – those folks who are owners of the processes should be there to see what the FDA investigator has to say about their area. Some investigators will give a pretty detailed out-briefing. Others will simply say, 'Here it is. Take a look at it, and if you have any questions, I'll answer those.' So, you can get any variety of close-out meeting with the agency.

"You have to be conscientious about what you are doing, what you are going to achieve. A show of strength probably isn't the best thing to leave in the investigator's mind. He or she will likely go back and tell their supervisor, 'I think these people are going to fight with us about everything from here on out.' A close-out meeting isn't an opportunity to put your heel on an investigator's throat and beat your ideas into them before they leave. It certainly isn't a chance to say goodbye and good riddance to their face."

Chase: "If an investigator comes back and tells their manager, the director of investigations, 'You know what? I had this close-out with this company, and they gave me the proverbial finger, and they basically said, "I don't really care what you have to say to me,"' I can bet you that FDA's compliance people are going to set a reminder on their calendar that says in 15 business days, they better be getting some correspondence from you. And if they don't, then, tick-tock.

"Because when you exhibit that type of behavior, basically what you're saying is, 'I'm not going to play in your arena. You can do and say whatever you want to do, but I'm not going to do it.' That's counterproductive and it doesn't work."

Published online 01/30/17

HiberGene's Rapid Group B Strep Test Pregnant With Potential

TINA TAN tina.tan@informa.com

Many may not have heard of Group B *Streptococcus*, but emerging Irish *in vitro* diagnostics company HiberGene Diagnostics Ltd. believes the life-threatening consequences of infections caused by this bacterium have carved out a potentially lucrative market. The firm launched its *HG GBS* rapid test at the end of last year to try to take advantage of the opportunity.

As an example, around 20%-30% of healthy adults in the UK are GBS carriers, without suffering side effects or showing any symptoms. The bacterium is typically found in the intestines, as part of the normal gut flora, but in women it can also reside in the vagina. In pregnant women who are GBS carriers, the bacterium can be transferred from the birth canal to their newborn babies during labor. Among these babies, about 700 each year in the UK alone, develop an infection caused by GBS. Around 10% of these babies with GBS-related infections will die, while up to a half of the survivors will suffer long-term mental and physical problems.

However, the risk of GBS infection in newborns can be significantly reduced by giving the mother intravenous antibiotics during labor. "Around two hours of antibiotics [delivered intravenously] has been found to be sufficient to protect the baby against GBS infection," Brendan Farrell, CEO of Dublin-based HiberGene, said in an interview.

But to know whether this preventative measure is required or not, the mother's GBS carrier status must be confirmed. To ascertain whether an expectant mother is GBS-positive, some countries, including the US, France and Italy – but not the UK and others – screen pregnant women at 35-37 weeks of their gestation period for GBS. There is also an increased move to perform intrapartum GBS testing, where the mother is tested when she goes into labor, and if she is positive, the antibiotics would then be administered to the mother.

Shutterstock: Andrei Shumskiy

HiberGene's HG GBS test can be used for any application or setting, Farrell indicated. "We can use the test for screening at 35-37 weeks, for intrapartum testing and also for testing the baby when it is born" to determine if it is a GBS carrier or not," he told *Medtech Insight*. The gold standard for GBS testing is the cell culture method, which requires a dedicated microbiology lab and promises turnaround times of up to 48 hours. The HG GBS test can be performed with minimal lab facilities and results can be obtained in around one hour, HiberGene says.

HG GBS – as with the other tests in HiberGene's portfolio, *HG Meningococcus* and *HG C.difficile* – runs on the *SWIFT* analyzer, a compact and portable desktop instrument that the company believes can be used by even labs with resource struggles. SWIFT uses loop mediated isothermal amplification (LAMP) to detect its DNA targets. Unlike standard polymerase chain reaction-based molecular testing techniques, LMAP does not require thermocycling and can run at a single temperature between 63-67 degrees Celsius.

The HG GBS test can be performed using any one of four types of samples: cerebrospinal fluid; whole blood samples form neonates; enriched broth from pregnant women; and vaginal swabs – HiberGene launched the HG GBS direct swab test in October 2016. Of the three settings in which HG GBS can be used (screening, intrapartum testing and neonate testing), Farrell believes that the biggest opportunity for HiberGene – and one that the company can capitalize on the fastest – is intrapartum testing.

The ease of sample collection using the HG GBS direct swab test and the fast turnaround time is particularly important for intrapartum GBS testing, Farrell pointed out. The results need to be known especially quickly for the antibiotics to be administered, if required, to the mother during labor.

Additionally, in a blinded study conducted by HiberGene and the National Maternity Hospital in Dublin, the performance of HG GBS was compared against cell culture. The results were positive, said Farrell: "HG GBS demonstrated its superiority over cell culture." Furthermore, the levels of sensitivity and specificity that were shown by HG GBS during the trial were compared against those of *Xpert GBS*, the GBS test offered by rival Cepheid. Here, HG GBS also beat out its rival, Farrell said.

The CEO was unable to reveal details of the trial's sensitivity and specificity outcomes, as the study results have been submitted to the European Congress of Clinical Microbiology and Infectious Diseases for presentation at the meeting in Vienna, Austria, in April. If the study is accepted, it will either be made public as an oral presentation or a poster at the congress.

DIRECT-TO-CONSUMER

While HiberGene's main target for its tests is the professional-use market, the firm also has a plan to target the consumer market with HG GBS. For this, the company has developed the *Strepelle* swab-sample collection kit for expectant mothers to use at home. Once collected, the swab samples would then be sent by post to

an NHS lab where the test is conducted. The result would be sent to the expectant mother by text and letter. If the results are positive and the patient finds out she is a GBS carrier, she can take this information to her caregiver, who will include this in the patient's management plan.

Currently, Strepelle is available to buy online (at £39.99/$50 a pack), but HiberGene is in discussions with several UK retail pharmacies, such as Superdrug, Morrison's and Tesco. Farrell told *Medtech Insight* that the main challenge is to maximize awareness about GBS within the pregnancy community. The company is using social media, and is exhibiting at midwife and baby shows to market its products, among other efforts.

PROFESSIONAL IVD MARKET STILL FIRST

While HiberGene may have decided to diversify into the consumer market for HG GBS, professional use is still the primary market the company is pursuing. For the last two years, the firm has been building its distribution network around the world, and it will continue to sign on more partners in what Farrell considers to be commercially promising geographic markets.

"There are IVD companies that sell to over 100 companies, but there are only about 80 countries in the entire world worth selling IVDs to. So our target is to get distributors in those 80 countries; we now have 36 countries covered and we're talking to potential distribution partners in another 25 countries."

With so many partners already in place, HiberGene's revenue growth is still modest. The company only made its first product sales in March 2016, following the launch of its first test, the HG Meningococcus for detecting bacterial meningitis. "We have had very little sales to date," Farrell acknowledged, "because the distributors wanted to wait until we had a test menu to offer. We now have three products in our portfolio, so we are getting over the inflection curve."

The company also plans to double the size of its portfolio with the addition of three new tests: a test for mycoplasma pneumoniae is expected to come out in April; one for flu A and B in the third quarter; and one for respiratory syncytial virus (RSV) 1 and 2 in the fourth quarter.

With a portfolio of six tests and an expanded distribution network by the end of 2017, HiberGene should be ready for accelerated growth next year. "We are building the business still and this will act as a springboard into 2018."

Published online 01/27/17

Verily Mulls Asian Acquisitions, Partnerships With $800m Temasek Cash

TINA TAN tina.tan@informa.com

Verily Life Sciences LLC, formerly Google Life Sciences, plans to expand its global reach through acquisitions or more partnerships, using an $800m cash injection from new Singapore-based investor **Temasek**.

Temasek has a $180bn portfolio across several industries, including health care, with around 69% of its investments rooted in Asia: 29% in Singapore and 40% in Asia outside Singapore. China is Temasek's second-largest market, making up 23% of its portfolio.

Verily spokesperson Carolyn Wang said that the US firm recognized that half of the future health-care consumers are in Asia and that the company was looking for "a sophisticated investor with a long-term horizon" – in line with the approach of Alphabet, Google's holding company – and with a deep network and experience in Asia. "Temasek has a deep understanding of growth economies in Asia, where it has significant longstanding interests and demonstrated success guiding its portfolio companies to overcome challenges and accelerate adoption of new technologies," she told *Medtech Insight*.

Verily will receive a majority of the $800m investment "in the coming days," and the remainder of the investment is scheduled for the second half of this year. Temasek will receive a minority stake in Verily and gain a seat on the board of directors. The Singaporean investor will advise Verily, said Wang.

Verily's publicly disclosed dealings with Asia to date include a collaboration with Nikon's division, Optos, to develop technology and solutions for enhanced screening of diabetes-related eye disease. Verily also has a distribution collaboration in Japan for its *Liftware* device, a smart spoon designed as an aid for people with motor disabilities. The spoon recognizes uncontrollable or unsteady hand movements at all times and automatically compensates, enabling people to eat without spilling.

Wang said that the proceeds from the investment could go toward supporting Verily's growth in key strategic areas, "including potential acquisitions, investment in partnerships and developing new opportunities on a global scale." The firm's current partners in health care include industry heavyweights like Johnson & Johnson in robotics surgery with the formation of Verb Surgical in December 2015; 3M Health Information Systems in health data management; Sanofi in diabetes management; and GSK in neuromodulation therapies, among others. "We're particularly interested in conditions that impact a large number of people where we believe technology can play a powerful role in provision of care," said Wang.

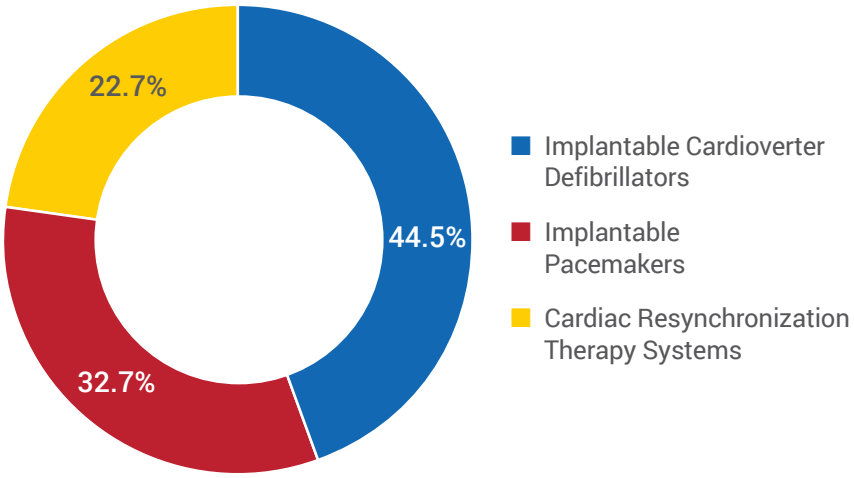
Temasek's interest is also expanding outside of Asia. Currently, North America, Europe, Australia and New Zealand collectively accounts for only 27% of the investor's portfolio. Temasek recently announced an increased focus on North American technology ventures, including health-care technology, and established an office in San Francisco in late 2016.

Published online 01/30/17

CONTINUED FROM PAGE 1

FIGURE 1

Estimated market share by product type for the global implantable CRM device market



Source: "Implantable Cardiac Rhythm Management Device Markets" (Meddevicetracker report)

market share of 25.3% and total attributable sales of $2.6bn. When it comes to CRM device sales for the forecast period 2015-2021, these European markets are expected to experience similar upward trends and downward pressures as their US counterpart.

Moving east, sales of implantable CRM products in Japan enabled the country to take an estimated 8.1% of the global market share. The remaining CRM product sales outside of the EU and US reached an estimated $2.2bn in 2015, and the emerging markets are also expected to show the strongest growth across all three CRM product segments over the forecast period.

TARGETING EMERGING MARKETS

Emerging markets continue to represent a huge opportunity for medtech manufacturers owing to improving income by a rising middle class, as well as access to health care, and greater awareness of medical procedures.

According to the *Meddevicetracker* report, the CRT, ICD and pacemaker product segments in these parts of the world are forecast to grow at a CAGR of 10.8%, 9.8%, and 14.2%, respectively. By comparison, the US is projected to see a CAGR of less than 3% across all three product segments.

Manufacturers of implantable CRM devices have already shifted their focus on these lucrative markets as a means to increase sales. The MDT report expects that the growth in these markets will reach beyond 2021 as more of the population will be able to afford access to such therapies as implantable CRM products.

COMPETITIVE LANDSCAPE

The major players in the CRM global market are Abbott Laboratories Inc., Biotronik SE & Co. KG, Boston Scientific Corp., LivaNova PLC and Medtronic PLC. While Abbott, Boston Scientific and Medtronic accounted for about 88% of total implantable CRM product sales in 2015, Medtronic remains the global market leader across all three product segments due to its diverse lineup of implantable CRM devices and strong marketing presence.

Abbott became an instant player in the CRM space on Jan. 4 when it finalized the $25bn acquisition of St. Jude Medical, which held the second biggest share of the CRM market, now part of Abbott's portfolio. *(Also see "Abbott Becomes CRM Player Overnight By Completing St. Jude Deal" - Medtech Insight, 5 Jan, 2017.)*

While the acquisition positions Abbott as one of the leading suppliers of cardiovascular devices globally, competing in almost all product segments, it isn't expected to have a large enough impact on sales to trigger a shift in global market share.

St. Jude's share of the CRM market has been slipping, especially in the US, because of competition from Medtronic and Boston Scientific, both of which offer MRI-conditional pacemakers, an important product differentiator that St. Jude lacks in its current product offerings. The delayed approval of St. Jude's first MRI-conditional pacemaker in the US will negatively impact US pacemaker sales and market shares for Abbott until the company receives approval from the FDA, according to MDT report projections.

In the European markets, privately held medtech company Biotronik managed to outsell Boston Scientific in the pacemaker and CRT segments in 2015, according to estimates in the *Meddevicetracker* report. The German-based company stands apart with a sizeable number of products – seven CRT models, five ICD models and six pacemaker models – offered throughout Europe, where Biotronik does a majority of its sales.

Looking ahead, limited variation in total market share by the key players through 2021 is expected amid the absence of new technologies, whose introduction and adoption would extend beyond the forecast period. For now, manufacturers of implantable CRM devices are expected to focus their product innovations on developing MRI-compatible models of existing products.

The key to increase product sales lies in expanding the number of eligible patients for CRM device implantation. Some of the limitations that manufacturers will need to address include inappropriate shock delivery, disruption of electrical signaling – which results in device malfunction in CRMs with strong magnetic fields – lead complications, and battery longevity and failure. Companies

that will be able to innovate in these areas will gain a competitive advantage in today's saturated marketplace.

ICDS LEADS TOTAL CRM SALES

In the global CRM market, in 2015, ICD was the dominating sector with $4.5bn in sales, a trend that is expected to continue with sales expected to reach roughly $5.6bn by 2021, a CAGR of 3.7%. (See Figure 2.)

The US was the global market leader in terms of ICD sales in 2015 with an estimated market share of 42.8% and corresponding product sales of $1.9bn; Europe ranked in second place with an estimated market share of 29.1%, followed by the emerging markets, which accounted for about 19.4% of total ICD sales; and Japan with 8.6% of ICD product sales.

Based on the *Meddevicetracker* report estimates, total ICD product sales will see the biggest growth in emerging markets at a CAGR of 9.8% from 2015 through 2021.

In 2015, Medtronic was the leading supplier of ICD products globally with an estimated market share of 40.7%. Abbott (previously St. Jude Medical) and Boston Scientific were the second- and third-leading suppliers of ICD systems with estimated market shares of 25.9% and 23.5%, respectively. Other suppliers of ICD products include Biotronik and LivaNova.

Figure 3 presents worldwide sales and market share data for the leading suppliers of ICD systems in 2015. (See Figure 3.)

BOSTON SCIENTIFIC'S S-ICD DIFFERENTIATOR

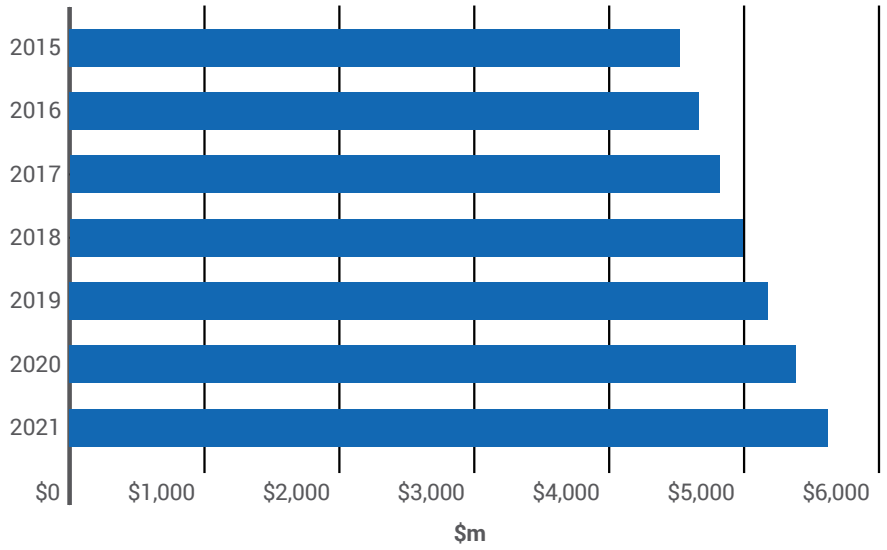
The approval of Boston Scientific's subcutaneous implantable defibrillator (S-ICD), which offers multiple advantages over conventional ICDs, is projected to give the company a significant boost in sales and a competitive advantage. *(Also see "Boston Scientific gets early nod for next-gen S-ICD" - Medtech Insight, 18 Mar, 2015.)*

The largest advantage of Boston Scientific's S-ICD is the lack of transvenous leads, which require an experienced surgeon to place properly and are also linked to increased morbidity. ICD implantation is also associated with complications such as cardiac perforation, systemic infection/endocarditis and valvular dysfunction. Compared to traditional ICDs, the S-ICD provides the proper subset of patients. It also has shown to have a lower risk of post-implant systemic infection, which makes it an ideal choice for patients with artificial heart valves or those receiving chronic immunosuppression therapy or hemodialysis. In addition, the S-ICD has also shown to be superior to conventional ICDs in terms of supraventricular arrhythmia discrimination.

The MDT report expects that Boston Scientific's device exclusivity will put the company on track to outpace competitors' sales. In addition, Boston Scientific also benefits from having an established product line, which will offer it a cushion if competitors follow the company's lead and develop comparable products.

FIGURE 2

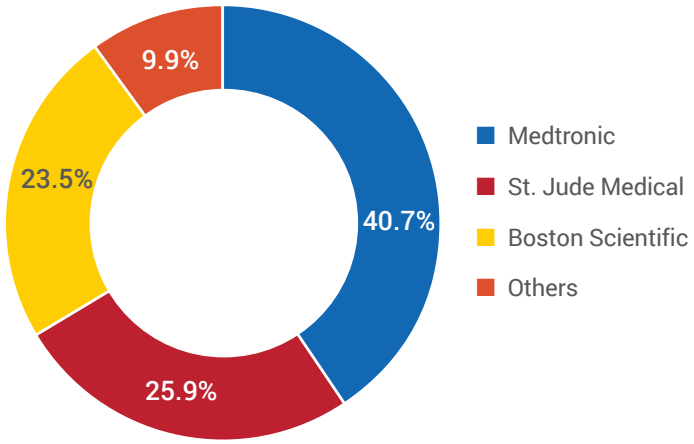
ICD Systems, Global Market Forecast, 2015-2021



*Source: "Implantable Cardiac Rhythm Management Device Markets" (**Meddevicetracker** report)*

FIGURE 3

Worldwide sales and market share data for the leading suppliers of ICD systems in 2015



Sales of ICD products will continue to be driven by the overall increase in heart disease rates, a growing demand for ICDs in emerging markets and improvements in diagnostics for diagnosing cardiac arrhythmias. At the same time, Medtech Insight expects several factors to drive down average sale prices in this space; chief among them are fierce competition among manufacturers, declining sales of ICD implants that aren't compatible with MRI machines, and improvements in battery longevity of ICD products, which lengthens the replacement cycle of these devices.

PROMISING FUTURE: LEADLESS PACEMAKERS

Meanwhile, the global implantable pacemaker market is expected to grow a modest 6% through 2021, rising in value from $3.3bn in 2015 to about $4.7bn by 2021. (See Figure 4.)

Of the total pacemaker product sales, the US was the leader with an estimated market share of 45%. As in other CRM product segments, the pacemaker market is expected to see modest growth in both the US and Europe (3.7%) through 2021 as the intense competition in these markets continues to drive down prices.

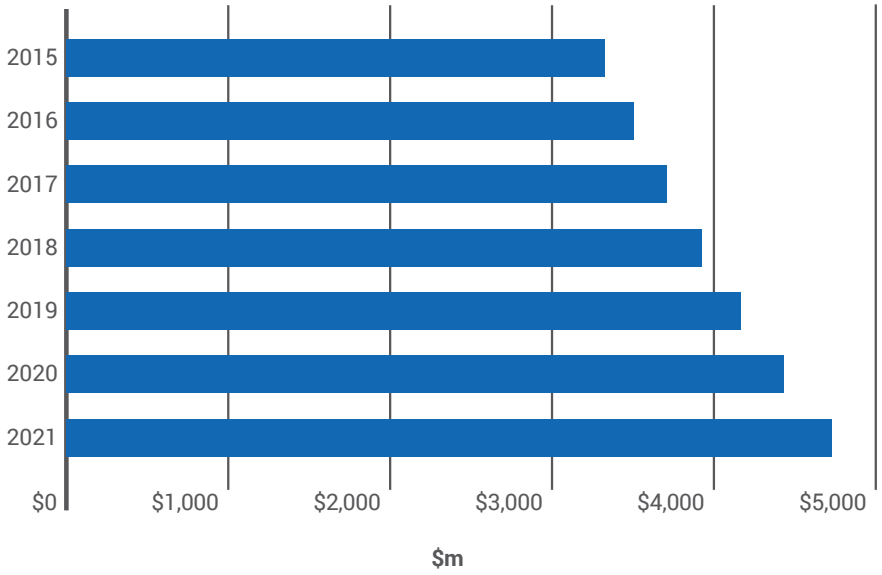
In the emerging markets, pacemaker sales are expected to witness double-digit growth of $14.2% through 2021, surpassing total product sales for Europe. In Japan, where a rising middle-class will also increasingly demand more sophisticated health-care services, the MDT report projects strong, single-digit annual pacemaker sales growth of 7.2%.

In terms of the competitive landscape for pacemaker products, Medtronic accounted for the largest global market share of total pacemaker product sales in 2015, followed by St. Jude (now Abbott) and Boston Scientific. Other manufacturers of implantable pacemakers include Biotronik and LivaNova. (See Figure 5.)

Growth in this product segment will be driven in large part by the rising heart disease rates (including arrhythmias) and demand for improved therapies in emerging markets, but technological innovations and improvements in arrhythmia-identifying diagnostics will also play a key role.

FIGURE 4

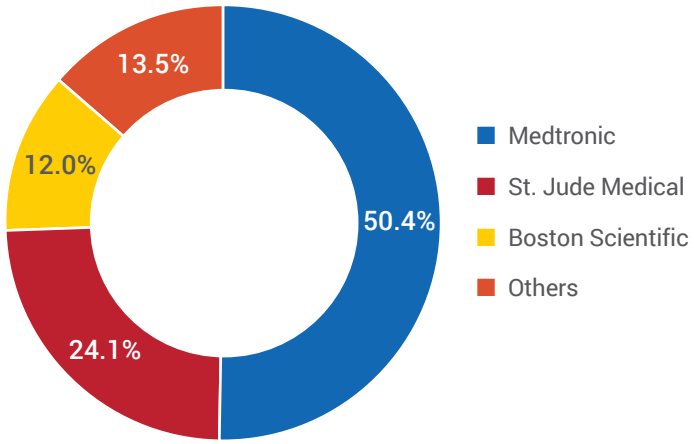
Pacemaker Systems, Global Market Forecast, 2015-2021



*Source: "Implantable Cardiac Rhythm Management Device Markets" (**Meddevicetracker** report)*

FIGURE 5

Worldwide sales and market share data for the leading suppliers of pacemaker systems in 2015



Technological innovations, such as device miniaturization and leadless pacing systems that provide more comfort for patients, among other benefits, are projected to reinvigorate pacemaker sales in the more mature markets. Also helping to revitalize pacemaker sales in mature markets is the introduction of MRI-compatible pacemakers, which will expand eligibility for pacemaker implants to patients who require MRI scans for concomitant diseases.

The top three players in the pacemaker market are all working on new pacemaker products, which will bolster future product sales. Medtronic was the first of the top three to receive regulatory approval in the US for its *Micra* leadless pacemaker. Boston Scientific is currently investigat-

ing its own leadless device, *Empower*, a modular pacing system that can be combined with the company's *Emblem S-ICD*, but has yet to start clinical trials. In October 2013, St. Jude acquired the rights to *Nanostim*, a leadless pacing system that received regulatory approval in Europe last March and is expected to receive FDA approval in 2017. The push from all three companies toward leadless pacing systems is also expected to help broaden patient eligibility for those who were previously ineligible for implantation with a transvenous pacemaker, which would further strengthen product sales in both mature and emerging markets.

As in other CRM segments, the chief limiting factor for pacemaker product sales in the US and Europe is competition among a limited number of players, which has resulted in downward pricing pressure. The focus on innovative products that address unmet needs would allow suppliers to command a higher selling price, which could potentially reverse the current trend in declining pacemaker prices.

CRTS POISED FOR SIGNIFICANT GROWTH IN EMERGING MARKETS

Meanwhile, the CRT device segment, which accounted for roughly 23% of total implantable CRM device sales in 2015, is also expected to see only modest growth. CRT devices are divided into two categories: CRT defibrillators (CRT-Ds) and CRT pacemakers (CRT-Ps). Of the two CRT devices, CRT-D product sales accounted for 83% of total sales in 2015. The global CRT device market is expected to grow 5.3% with sales rising from an estimated $2.3bn in 2015 to $3.1bn by 2021. (See Figure 6.)

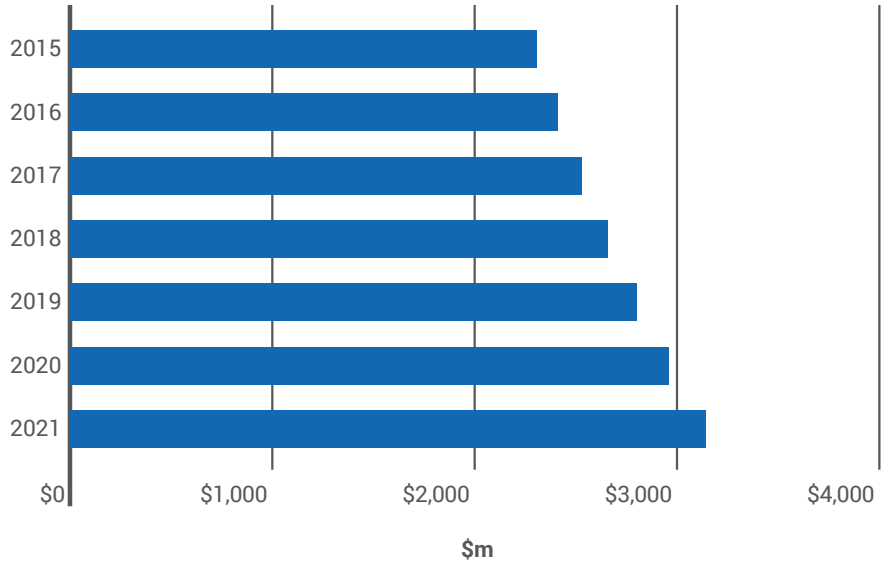
In 2015, the US accounted for nearly half, or 49.1% of total CRT systems sales. Compared to the ICD and pacemaker product segments, CRT product sales accounted for the second largest market share with 28.5% in the emerging markets in 2015. According to projections in the *Meddevicetracker* report, total CRT products sales in this region will only narrowly fall behind the US by 2021.

Sales of Medtronic CRT products accounted for an estimated 49.5% of global CRT product sales in 2015, followed by St. Jude (now Abbott) in second place and Boston Scientific in third. Other manufacturers of CRT devices include Biotronik and LivaNova. (See Figure 7.)

Overall growth of CRT sales will be supported by similar driving forces and face similar challenges as the other CRM segments. When it comes to the CRT market, however, it is anticipated that this segment will also face competition from such alternative heart failure therapies as coronary artery bypass grafting, percutaneous coronary intervention, medical management with pharmaceutical therapies, valve replacement and heart transplantation.

FIGURE 6

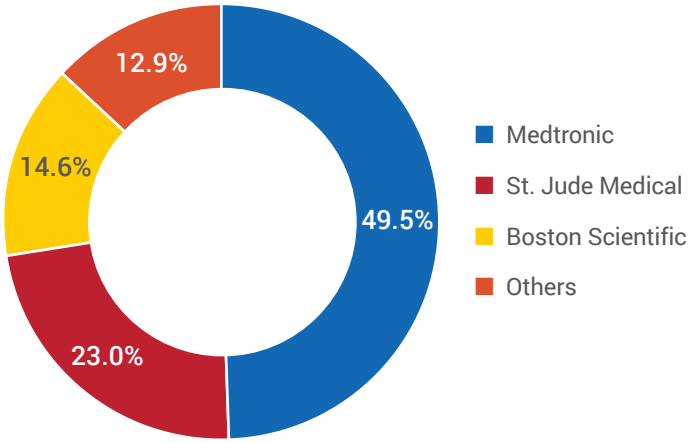
CRT Systems, Global Market Forecast, 2015-2021



*Source: "Implantable Cardiac Rhythm Management Device Markets" (**Meddevicetracker** report)*

FIGURE 7

Global CRT Systems Market, Share by Supplier, 2015



*Source: "Implantable Cardiac Rhythm Management Device Markets" (**Meddevicetracker** report)*

Published online 01/30/17

Medtech Insight
Pharma intelligence | informa

advertise with us and take your business to the next level.

you won't believe the transformation

Contact our sales executive to learn about our various advertising opportunities available to you!

Christopher Keeling
+44 203 377 3183
christopher.keeling@informa.com
Customer Care: +1 888-670-8900 (USA)

medtech.pharmamedtechbi.com

Over 100 event types

Over 100 catalyst types

Over 5,000 products

Meddevicetracker
Pharma intelligence | informa

Double **the Power**

Meddevicetracker with Medtech Insight reports is a new interactive real-time source of in-depth medical technology market intelligence

Meddevicetracker brings you closer to the medtech market, helping you to:

- Identify upcoming device regulatory events/filings
- Search for medtech clinical trial starts and data
- Find historical and forecasted procedure volumes data
- Monitor drug delivery technologies and identify partnership opportunities
- Quantify the market size for devices or diseases
- Discover forecasted market share of devices by type
- Understand the device competitive land-scape and identify unmet clinical needs

Request your free demo today:
please visit - **www.meddevicetracker.com**