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MDR REPORTING:

FDA Embraces Adverse Event Summaries Under MDUFA IV, But Flouts Similar FDAAA Mandate

SHAWN M. SCHMITT shawn.schmitt@informa.com

US FDA appears to be embracing an increase in summarized Medical Device Reports from industry under the upcoming MDUFA IV user-fee agreement, while turning a cold shoulder to a more watered-down summary report requirement found in a decade-old congressional act.

Laid bare in an August draft Medical Device User Fee Amendment IV commitment letter, the agency will allow makers of a majority of devices to report adverse events quarterly under FDA's Alternative Summary Reporting Program rather than individually on full MedWatch reporting forms. Summary reporting allows device firms to submit abbreviated reports in a summarized, line-item format.

FDA and industry groups came to an agreement on the MDUFA IV commitments and user-fee structure this summer. The commitments will be paired with reauthorization legislation that Congress must pass later this year in order for the device user-fee program to continue.

"For most, if not all, device procodes, FDA will permit manufacturers of such devices in those procodes to report malfunctions on a quarterly basis and in a summary MDR format," the MDUFA letter confirms. "FDA will publish the list of eligible device procodes within 12 months of receiving a proposed list from industry."

The list of devices eligible for summary reporting will include high-risk class II and class III products, and be maintained on FDA's website. Devices that fall under a procode in existence for fewer than two years might, however, not be allowed to report in summaries; that will be left to FDA's discretion. Further, events that involve a death cannot be filed in summaries.

"The agency has been moving toward less pre-market information and more post-market information so it can get innovative devices to market quicker. FDA is asking for less data upfront and more data on the backend," explained Sonali Gunawardhana, a former FDA device center regulatory counsel who is now an attorney at Wiley Rein.

"When FDA gets MDR summaries, it kind of gives FDA more of an idea of exactly how a device is working once it's been deployed into the field," she told

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VC investing in 2016
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Venture investment activity ceased its year-on-year growth and fell for the first time in 2016. Take a deeper dive into the VC investing landscape that companies were faced with last year, and which sector benefited the most from investors' generosity.

Partnerships and alliances
http://bit.ly/2jDyfiT

The latest instalment of our bimonthly Pacts In Medtech column looks at a particularly long list of collaborations and alliances forged between players in the medical devices and diagnostics industry.

FDA hits wall with software guideline
http://bit.ly/2j1wI35

The US agency wanted to boost regulatory harmonization by adopting an international guideline on device software, but got industry blowback instead.

Device tax attack
http://bit.ly/2j7UnBG

AdvaMed and MDMA, two rivaling lobby groups, have again come together against a common enemy: the Obamacare medical device excise tax.

Device Week
http://bit.ly/2iGiSlX

Our weekly podcast, where *Medtech Insight* journalists discuss topics they are covering that impact the device and diagnostics sector.

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from being unnecessarily withdrawn from the EU market following the exit of notified bodies from the medtech sector. But will this practical solution mean some CE-marked products will be floating freely around Europe with no notified body backstop?

15 **3D Printing Opens A Legal Brave New World –** Attorneys at Reed Smith have released a white paper that attempts to tackle the legal uncertainties facing 3D printing of medical devices. They tackle issues including product liability, intellectual property and quality management.

16 **FDA Moves Mesh Surgical Instrumentation Up To Class II In Final Order –** The US agency has agreed with an earlier assessment by an advisory panel last year to up-classify surgical mesh instrumentation by issuing a final order to move the instrumentation – used for women undergoing pelvic organ prolapse or female stress incontinence procedures – from class I to class II.

17 **Bone Anchor 510(k) Guidance Gets Update –** US FDA has revised and expanded its 1996 guidelines on bone-anchor submissions. The revision discusses clinical and nonclinical testing standards for devices used to fasten tissue to bone, as well as other 510(k) concerns.

COMMERCIAL

18 **Abbott Becomes CRM Player Overnight –** Abbott Laboratories has finalized its $25bn takeover of St. Jude Medical, first announced in April, making Abbott a major player in almost every corner of the $30bn cardiovascular device market.

19 **Court Revives Medtronic Stock Fraud Case –** Three pension plans sued the company on the grounds that it hid risks posed by the off-label use of the Infuse bone cement product. The case was dismissed by a lower court last fall as having been filed outside the statute of limitations, but the Eighth Circuit Court of Appeals ruled the claims to be valid.

19 **Philips, Illumina Sign Genomics For Cancer Pact –** Philips and Illumina are teaming up to develop a connected solution for the analysis and interpretation of genomic information in cancer.

CLINICAL TRIALS

20 **Starts & Stops: S-ICD And Respiratory App Studies Among Year-End Large-Scale Trial Launches –** Starts & Stops is a regular feature highlighting Medtech Insight editors' picks of noteworthy medtech clinical trial initiations, completions and suspensions over the past month. This edition notes the particularly high number of large-scale trials launched toward the end of 2016.

M&A ANALYSIS:

Underwhelming 2016, But Hope For 2017 US Market Boom

CATHERINE LONGWORTH catherine.longworth@informa.com

A final flurry of activity in December rounded off 2016 with a tally of 174 medtech M&A deals, a year-on-year decline from the 237 deals tracked by *Medtech Insight* in 2015 and 269 in 2014. But while total deal volume in 2016 waned from previous years, 2017 could signal a potential bounce-back.

The changing political landscape in the US could have a weighty impact on domestic M&A activity, according to Mick Cooper, analyst at boutique research firm Trinity Delta. "It all depends on whether Donald Trump pushes through repatriation of money to the US from overseas," he said. "If he does, that could lead to more M&A activity in the US this year, but we will have to wait and see what policy changes he brings in."

Conversely, if money is redirected from Europe back to US soil, this could have a "long-term negative" impact on the European health-care sector, Nick Keher, director of health-care equity research at RBC Capital in London, told *Medtech Insight* shortly after the US presidential election in November.

Cooper added that 2017 could see the return of big-bucks deals, including the potential acquisition of orthopedics giant Smith & Nephew, which has long been dogged by rumors of an acquisition by Stryker.

He added that there may be continued interest in modest acquisition targets: "The big companies always need new ideas that come out from small companies so they're always looking for bolt-ons to revitalize their portfolios."

"In 2017 we could see French companies like **Vexim, Spineguard** and **Medicrea** as targets for acquisitions. All of these companies have interesting niche products that, depending on their sales traction, could get snapped up to add on to bigger companies' portfolios. However, they also don't have the type of portfolios that can reinvigorate a franchise. Sports medicine is also one sector that is really growing, so companies in this realm are attractive targets for acquisition in 2017."

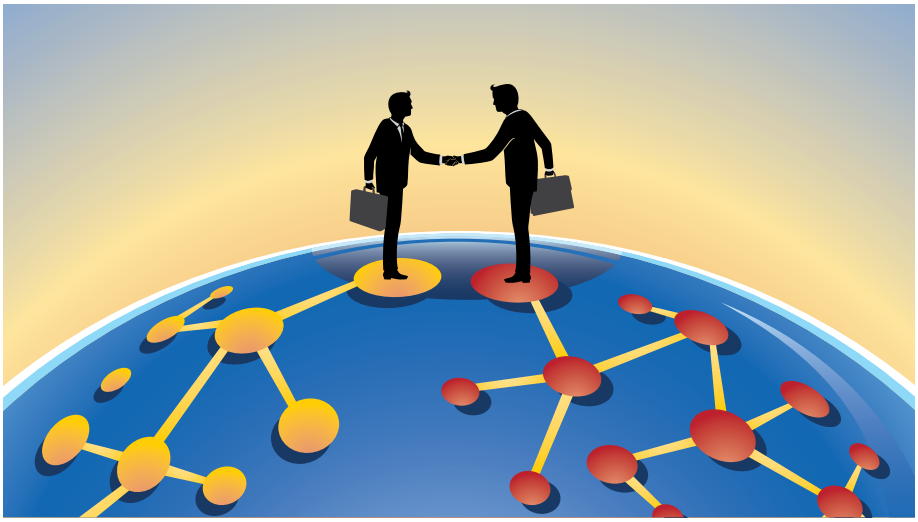

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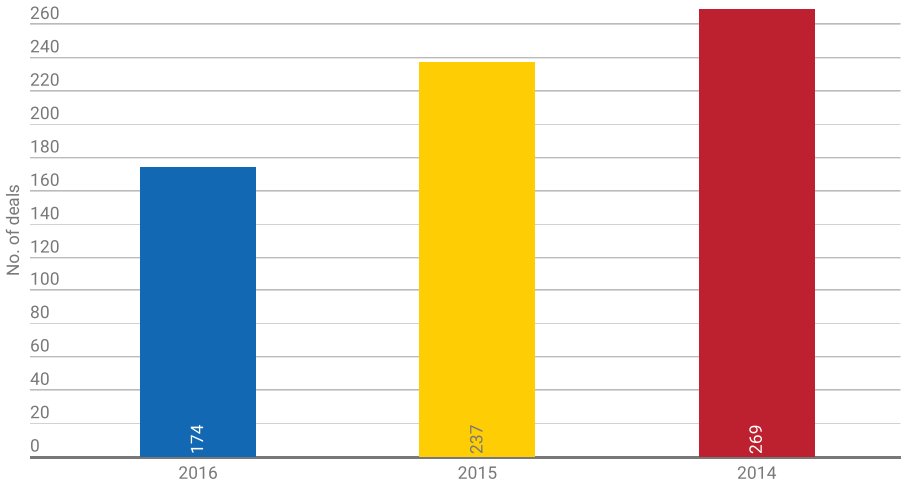
FIGURE 1

M&A deal volume 2016 vs 2015 vs 2014



Source: Medtech Insight M&A data tracker

Indeed, 2016 saw interest in bolt-on deals from big players. British company **Phagenesis** entered into a staged acquisition by **Nestlé Health Science**. The company, which was formed in 2007, has developed a device for the treatment of dysphagia, which is the inability to swallow.

Zimmer Biomet also snapped up sports medicine business **Cayenne Medical** for an undisclosed amount, while US company **Agilent Technologies** agreed to buy University of Antwerp spin-out Multiplicom for €68m. The Belgian diagnostics company started commercializing its clinical lab test kits for DNA amplification in 2011.

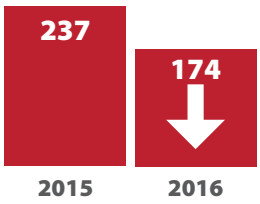
BIG DEALS STILL THERE

2016 saw 11 billion-dollar acquisitions, compared to 18 in 2015. However, despite deal value and volume dipping in

Medtech M&A Deals 2016

A snapshot of the industry's mergers and acquisitions in 2016.

Medtech M&A activity was down in 2016 from 2015 numbers.



TOP 3 DEALS

$25bn
Abbott was the biggest spender of the year with St. Jude.

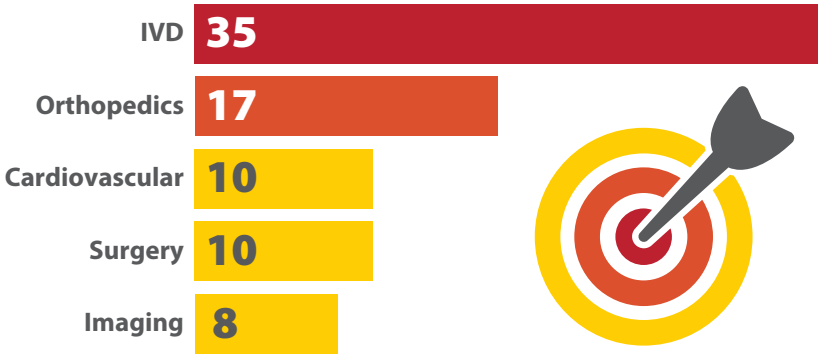
$4.33bn
J&J's acquisition of Abbott Medical Optics.

$4bn
Danaher's deal to buy Cepheid.

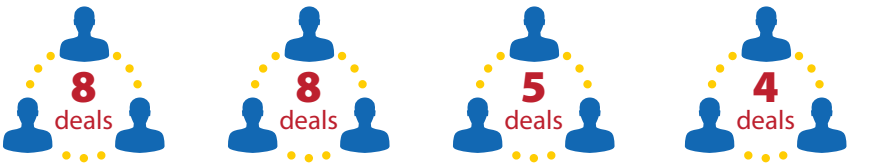
BILLION VS MILLION $ DEALS

11 billion-dollar deals scored in 2016, compared to 77 million dollar deals.

In-vitro diagnostics was the most popular target for M&A in 2016. There were 35 IVD deals in 2016, compared to 48 IVD deals in 2015. Overall, M&A activity in medtech sectors was relatively consistent in 2016 and 2015.



Stryker and Zimmer Biomet scored the highest number of deals in 2016, with both companies picking up 8 companies each, followed by Medtronic and Boston Scientific.



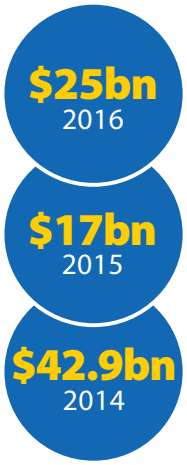
DEEPEST POCKETS OF 2016

Abbott splashed the most cash with its $25bn St Jude deal. It also bought electrophysiology company Kalia for an undisclosed amount.

Zimmer Biomet disclosed one major billion-dollar deal and a $130m agreement to buy French orthopedics company Medtech SA.

Stryker made two billion-dollar deals and disclosed another one worth $52m.

BIGGEST DEALS YOY



Abbott acquisition of **St Jude Medical**.

Pfizer acquisition of **Hospira**.

Medtronic acquisition of **Covidien**.

Abbott announced the biggest acquisition of the year with its $25bn takeover of St Jude Medical. The deal closed on 04 January 2017.

2016, the year saw one blockbuster transaction with **Abbott Laboratories Inc.** tabling a $25bn deal to acquire St. Jude Medical. The agreement, which had been set to close before the New Year but was completed on Jan. 4, was the biggest transaction to be inked in 2016. It topped the winner in 2015 – **Pfizer Inc's** $17bn takeover of **Hospira Inc**. However, neither 2016 or 2015 could match the might of 2014, which saw Medtronic's mega $42.9bn buyout of Covidien Plc. The latter remains the largest M&A transaction in medtech history.

Other notable big buyouts of 2016 included **Danaher Corp.'s** $4bn acquisition of **Cepheid** Danaher paid a 54% premium to acquire Cepheid, maker of the fully automated *GeneXpert* rapid genetic testing system. Cepheid joined Danaher's $5bn diagnostics segment, which includes Beckman Coulter, Leica Biosystems and Radiometer.

Medtech giant **Johnson & Johnson** also paid big bucks to pick up **Abbott Medical Optics Inc.**, Abbott's ophthalmic surgical division, for $4.33bn to bulk up its vision-care assets.

In addition to St. Jude, Abbott had another acquisition in the pipeline, a $5.8bn deal for IVD group **Alere Medical Inc.**, which was signed early in Jan. 30. However, the merger soon hit the brakes after a series of financial and regulatory errors by Alere surfaced. The two companies are embroiled in a legal wrangle, with Abbott filing a suit on Dec. 7 in Delaware Chancery Court, claiming Alere's missteps made finalizing the merger impossible.

Other billion-dollar M&A transactions of 2016 included **Thermo Fisher Scientific Inc.**'s $1.3bn takeover of IVD cellular and genetic company **Affymetrix Inc.**, and **Zimmer Biomet Holdings Inc.**'s deal to buy **LDR Holding Corp.** for $1bn. **Stryker Corp.** also picked up **Sage** for $2.28bn, and **Physio-Control Inc.** for $1.28bn.

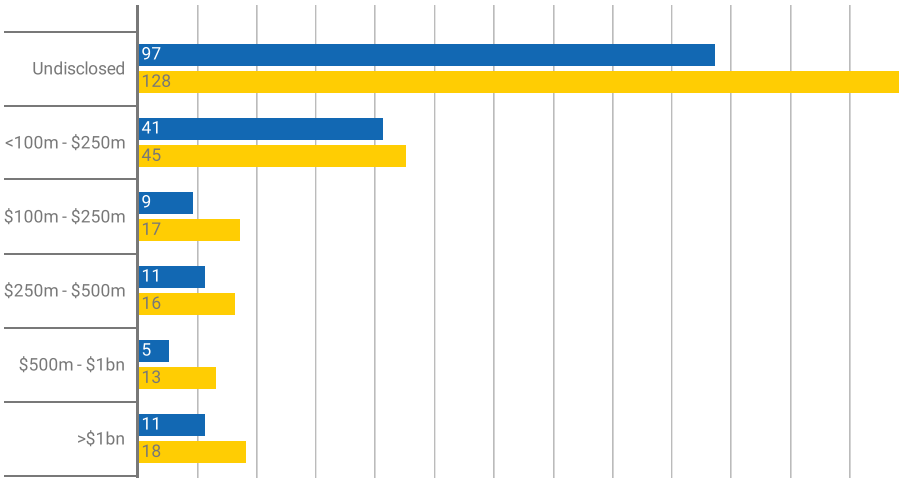
EAST MEETS WEST

2016 saw continued investment by Asian companies in Western assets, with two Chinese companies targeting US companies for takeovers. **Sinocare Inc.** picked up US point-of-care diagnostics **PTS Diagnostics** for $290m, and **Venus MedTech (HangZhou) Inc.** acquired **Transcatheter Technologies GMBH's** portfolio. Singaporean company **Vela Diagnostics** also bought next-generation-sequencing diagnostics firm **Lifecode Inc.** for an undisclosed amount. That said, M&A activity in the Chinese markets was notably lower than 2015, fitting with the overall M&A volume decline in 2016.

An example of European companies spreading eastward, noninvasive prenatal-testing specialist **Premaitha Health PLC** made a deal to acquire Taiwanese company **Yourgene Bioscience Co. Ltd.** in December. The total deal price was approximately £7.2m, which will be funded through a cash-and-stock mix.

FIGURE 2

Mergers & acquisitions by value 2016 vs 2015



Source: Medtech Insight M&A data tracker

POPULAR SECTORS

IVD companies continued to be the medtech space's most popular target for acquisition with 38 IVD deals in 2016, compared to 48 deals in 2015. Orthopedics proved to be the next most popular medtech sector with 17 deals. This was a rise on the 13 orthopedic deals made in 2015, and mainly due to major spending sprees by orthopedics giants Stryker and Zimmer Biomet. However, although cardiovascular remained as one of the most popular sectors, deal volume dipped from 23 in 2015, to 10 in 2016.

On the whole, M&A deal activity stayed relatively consistent in 2016 compared to 2015. Cardiovascular, imaging and surgery all continued to be the more popular sectors for consolidation.

As for the year's biggest shoppers, Stryker and Zimmer Biomet both snatched the crown from Medtronic, which earned the title in 2015. The two ortho-players scored eight acquisitions apiece, one less than the nine Medtronic bought in 2015.

However, Medtronic still did some spending in 2016, adding five companies to its business, while Boston Scientific followed with four acquisitions under its belt, including a $75m cash deal at the end of the year to buy Canadian biological tissue business Neovasc.The company will be integrated into Boston Scientific's structural heart business for use in the manufacturing of its *Lotus Valve System*.

But can 2017 meet hopes for a market boom? It may shape up to be a positive year for the US medtech market depending on President-elect Trump's policy changes. In Europe, the year will be punctuated with several key elections across the continent, including in France, Germany and the Netherlands, that could cause turbulence in the markets. Plus, if US threats of cash repatriation ring true, then European companies may find themselves looking to the Asian markets for revival.

Published on 01/06/2017

FDA Recommends Security Patch For St. Jude Wireless Cardiac Devices

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US FDA issued an alert Jan. 9 for **St. Jude Medical Inc.** cardiac devices that link to its *Merlin@home* transmitters. The agency said there's a risk for malicious attacks that could "harm" patients and urged users to install a software patch on their devices to minimize the risk.

The alert comes months after short-sale investment firm Muddy Waters Research and security research firm MedSec published reports and videos of their ability to break into the devices and cause them to malfunction, as well as deplete their battery.

St. Jude has vehemently denied the extent of the threat to its devices and has accused Muddy Waters of stoking fear in order to make a profit. The company even announced in September it was suing the investment firm.

Muddy Waters, however, has maintained that St. Jude's devices are dangerously vulnerable and has urged FDA to issue a recall. With FDA's latest alert, the company says it feels vindicated.

Carson Block, founder of Muddy Waters, says the acknowledgment by St. Jude that there is a vulnerability with their devices just days after completing a sale to Abbott Laboratories reaffirms his views that the company puts profits over patients.

"It also reaffirms our belief that had we not gone public, St. Jude would not have remediated the vulnerabilities," he said in a company statement. "Regardless, the announced fixes do not appear to address many of the larger problems, including the existence of a universal code that could allow hackers to control the implants."

Asked by *Medtech Insight* to provide more details, the company said it could not do so due to the impending lawsuit it is currently fighting with St. Jude.

The safety alert from FDA states the agency confirmed the cybersecurity vulnerabilities associated with St. Jude's Merlin@home transmitter could give unauthorized users control over the company's radio frequency-enabled implanted cardiac devices, and allow those with malicious intent to deplete battery on those devices and/or change their pacing or shock the patient.

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While Muddy Waters has warned that the vulnerabilities could potentially kill patients, FDA only states it could harm them. While high-risk class I recalls often note that they are issued because there is a possibility of death, it does not always do so in safety communications.

FDA, however, still asserts that no patients have been reported harmed by the vulnerability and that the benefits of using the devices outweigh the risks. It advises users of the devices to connect to the company's servers in order to download and install a software patch to limit malicious hackers from breaking in.

"To improve patient safety, St. Jude Medical has developed and validated a software patch for the Merlin@home transmitter that addresses and reduces the risk of specific cybersecurity vulnerabilities," stated the agency. "The patch, which will be available beginning Jan. 9, 2017, will be applied automatically to the Merlin@home transmitter. Patients and patient caregivers only need to make sure their Merlin@home transmitter remains plugged in and connected to the Merlin.net network to receive the patch."

FDA says it reviewed the patch to ensure it has addressed the greatest risks posed by the vulnerabilities and reduce risks of exploitations. The agency emphasizes such vulnerabilities are not unique to St. Jude and many medical devices could have similar vulnerabilities. It also says as medical devices become increasingly interconnected via the internet, hospital networks, other medical devices, and smartphones, there is an increased risk of hackers exploiting vulnerabilities and causing them to function improperly.

"Any new cardiac devices submitted to the FDA for review by St. Jude Medical that use the Merlin@home transmitter will not be cleared or approved without the Merlin@home software update installed and without adequate assurance that appropriate cybersecurity controls are in place," said FDA spokeswoman Angela Stark.

St. Jude spokeswoman Candace Flippin says the company is continually providing

updates to the Merlin@home system, having released seven software updates in just the past three years. The latest patch includes communication validation and verification capabilities between the device and its Merlin.net servers that were developed in collaboration with FDA and the Department of Homeland Security's Industrial Control Systems Cyber Emergency Response Team (ICS-CERT). She says the company plans to issue more updates in the coming year.

"As medical technology advances, it's increasingly important to understand how innovation and cybersecurity impact physicians and the patients we treat," said Leslie Saxon, chair of St. Jude Medical's Cyber Security Medical Advisory Board. "We are committed to working to proactively address cybersecurity risks in medical devices while preserving the proven benefits of remote monitoring to assess patient status and device function."

While so far FDA says it has not recorded any incidents of patients being harmed by cyber vulnerabilities, there have been a number of cases where hackers have discovered such risks. As a result, top lawmakers on the House Energy and Commerce Committee wrote to FDA asking what the agency is doing to ensure that devices are protected against malicious hackers.

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Califf Sets Departure From US FDA; Ostroff May Become Interim Leader

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Robert Califf has formally scheduled the end of his time as FDA commissioner and it appears a familiar face might temporarily take his place.

Stephen Ostroff, deputy commissioner for foods and veterinary medicine, appears in line to become the temporary acting commissioner, assuming Califf departs as scheduled and the incoming Trump administration does not designate someone else to run the agency in the short term. It was Ostroff who served as the bridge between the end of Margaret Hamburg's tenure in April 2015 and Califf's confirmation in February 2016.

Candidates who have been mentioned as possible Trump picks to head FDA include Jim O'Neill, a Silicon Valley investor and Libertarian, and former FDA and Centers for Medicare and Medicaid Services (CMS) official Scott Gottlieb, who was added to the Trump Health and Human Services (HHS) transition team in November.

Typically, political appointees like Califf resign their positions when a new president is elected, but it is possible they could ultimately retain their jobs.

OSTROFF HAS WEIGHED IN ON DEVICE ISSUES

The HHS employee directory lists Ostroff as acting commissioner, although it is unclear whether his entry has not been updated since he last held the acting commissioner title. Califf does not appear in the directory.

Ostroff has been a longtime champion of medical product innovation, as well as a spokesperson for device safety; he addressed both issues last year in a January 2016 blog post shortly before Califf's confirmation as commissioner. In the 2016 letter and other FDA blog posts, he highlighted FDA's investigations of fraudulent medical products marketed to diagnose, prevent and treat Ebola, as well as the agency's efforts to bring PMA-approved devices to market more quickly.

The acting commissioner also led FDA's efforts to respond to duodenoscope contamination issues in mid-2015 after Hamburg's departure by kicking off a high-profile two-day public advisory panel meeting on duodenoscope and endoscope safety and reprocessing in mid-May 2015. He also authorized FDA's follow-up post-market surveillance study orders on the scopes.

CALIFF WILL STAY UNTIL INAUGURATION DAY

FDA said in a recent email that Califf will leave the agency at noon on Inauguration Day (Jan. 20), as per presidential transition tradition.

Typically, political appointees like Califf resign their positions when a new president is elected, but it is possible they could ultimately retain their jobs. Califf has said several times that he would like to continue as commissioner under the Trump administration, although it is rare for a commissioner to survive a change in White House occupants. Califf was thought to have a chance because of his overwhelmingly bipartisan confirmation vote.

Califf joins Office of Criminal Investigations Director George Karavetsos, who also has announced he will leave his post on Inauguration Day.

Other political hires at the agency also likely will depart within the next few weeks.

Published online 01/06/17

FDA Provides Accessories Guidance, But May Be 'Missed' Opportunity

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US FDA issued final guidance to help sponsors better understand how the agency intends to classify accessories to devices. But one industry group leader says the document fails to provide the clarifications that companies in the software space, at least, were looking for, and doesn't address many accessories already on the market.

The guidance, posted Dec. 29, finalizes a draft version issued early in 2015. The final document sticks with the overall approach laid out in the draft, concluding that an accessory should be classified based on its intended use, which might put it in the same or lower risk category as the parent device. This approach, FDA notes, was buttressed by the recently enacted 21st Century Cures Act.

"On December 13, 2016, section 513(b) of the FD&C Act was amended by the 21st Century Cures Act (Public Law 114-255) to state that the 'Secretary shall classify an accessory … based on the intended use of the accessory, notwithstanding the classification of any other device with which such accessory is intended to be used,'" states the guidance. "Accordingly, the classification of accessory devices, as for non-accessory devices, should reflect the risks of the device when used as intended and the level of regulatory controls necessary to provide a reasonable assurance of safety and effectiveness."

MORE DETAILS SOUGHT

The guidance explains that any device intended to "support, supplement and/or augment" a parent device could be considered an accessory.

But industry was hoping that the final guidance would fill in more information gaps, says Bradley Thompson, an attorney with Epstein Beck Green who represents the Clinical Decision Support Coalition, a group of companies whose technologies often work with other devices.

The guidance isn't the agency's "best work" and leaves a lot of unanswered questions, Thompson laments.

"I suppose, by definition, any article that does not do one of those three things is therefore not an accessory," he told *Medtech Insight*. "But FDA spent almost no ink explaining what the world outside of those categories looks like. Repeatedly, commenters requested more examples and more explanation for product categories such as connected health."

Thompson says the lack of clarification, in his view, is challenging to manufacturers that may not be confident what the agency expects of them.

"FDA missed the opportunity to help industry by responding to comments requesting more examples," he added. "It would've been a relatively simple matter to go through a list of common products and explain how that three-part test is applied. Despite the request in the comments, FDA did not do so."

It feels like FDA, upon passage of the Cures legislation, decided to move this through quickly before the end of the year," attorney Brad Thompson says.

PATH TO DOWN-CLASSIFICATION?

Thompson wonders if the guidance was rushed out. He notes that the document mentions the Cures Act, but the agency allowed itself three weeks to weigh the impact on the legislation on its authority.

"It feels like FDA, upon passage of the Cures legislation, decided to move this through quickly before the end of the year," Thompson said.

"It's unfortunate, because the comments made a number of good suggestions about improvements that would've made the document much more useful going forward," he added. "Unfortunately, it doesn't look like FDA gave either the legislation or the comments on the draft guidance much thought."

While Thompson says the guidance is very helpful in establishing that an accessory doesn't have to be regulated in the same class as the parent devices, he worries it only deals with new accessories. In particular, the guidance emphasizes use of the *de novo* process to classify new accessories. But, he notes, the guidance doesn't do much to address the plethora of accessories already on the market.

"While there will always be hopefully a stream of new accessories in the future, there are a huge number of accessories already on the market today that are effectively overregulated because they are placed in the same classification as the parent," said Thompson. "The document pays no attention to those existing accessories, nor does it provide any regulatory avenue for down-classifying those accessories. That's a big miss for FDA, and leaves industry in the dark about what to do concerning these presently overregulated accessories."

He says FDA needs to provide a practical way for manufacturers of existing accessories to down-classify their products without excessive costs to them or to the agency.

FDA spokeswoman Deborah Kotz says FDA and industry committed to working together on coming up with an appropriate process for reclassifying existing accessories during the recent Medical Device User Fee Amendment (MDUFA) IV negotiations.

"The FDA will work with industry to explore additional mechanisms to reclassify accessories previously classified as class III devices ... if they meet the requirements of a low- or moderate-risk device," she said in an email.

However, Kotz declined to comment on whether FDA is working on any future guidance to tackle the subject.

Thompson is also concerned that FDA's use of the *de novo* process for all accessories could be time-consuming and expensive, especially for manufacturers of low-risk medical device accessories. As an example, he says a newly designed pole to hold infusion pumps would be put in the same category as the pump, and the burden to bring such a product to market would be too high.

"Under this guidance, if you are the first to develop that pole, it will be placed in the same classification as an infusion pump until you pursue the *de novo* process," said Thompson. "It's a pole. It holds things up in the air. Does FDA seriously want manufacturers to take products like that through the *de novo* process? As with old accessories, for new accessories we need a better way of appropriately classifying them without imposing a process that is very much akin to a PMA."

Kotz says such stands for infusion pumps are already categorized as class I devices, but did not delve into what that means for new types of stands that may be significantly different than previous stands.

The guidance is also not clear enough about the real-world distinction between device components and accessories, Thompson says.

FDA does clarify to sponsors that components are any raw material, substance, piece, part, software, firmware, labeling, or assembly that is intended to be included as part of the finished, packaged, and labeled device. By definition, these are not considered accessories, which are finished devices.

This clarification doesn't do enough to take into consideration how such products are treated in the real world, Thompson says.

"Often components are finished in the sense of being complete in and of themselves," he said. "Traditionally, the distinction between an accessory and a component is not so much the state of the product, but to whom it is sold. Accessories are sold the end users, where components are sold to manufacturers for incorporation into a product. But FDA didn't go into that."

FDA and industry committed to working together on coming up with an appropriate process for reclassifying existing accessories during the recent user-fee negotiations, an agency spokeswoman said.

SOFTWARE AS A MEDICAL DEVICE

One new element in the final guidance is a statement that FDA intends to oversee software accessories that could be considered software as a medical device (SaMD), a topic not mentioned in the draft version.

In the final guidance, the agency says FDA is using the interpretation of SaMDs as laid out by the International Medical Device Regulators Forum (IMDRF) to oversee such products.

The agency's guidance complements an August draft guidance that outlines when sponsors should file 510(k)s for modifications to software embedded in medical devices, software that act as an accessory to other devices or when the software stands alone.

While SaMDs that meet the definition and use data from medical devices don't automatically become accessories under the guidance, the agency intends to regulate some software that could be used in combination with medical devices.

"Regardless of whether a SaMD uses data from other devices or is used in combination with other devices, the FDA intends to apply the same risk- and regulatory control-based classification paradigm discussed in this guidance to all software products that meet the definition of SaMD and also meet the definition of an accessory," states the agency.

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CONTINUED FROM PAGE 1

Medtech Insight. "That's why the agency is asking for summaries: to give FDA a more comprehensive understanding of how the device is working every day."

In any given year, more MDRs are reported to FDA individually than in summaries. For example, nearly 1 million MDRs – 967,839 – were sent to the agency individually in 2015, while only 442,002 were sent as part of the Alternative Summary Reporting Program.

Although adding more summary reports might have the effect of reducing the overall total number of adverse event reports, Gunawardhana said that doesn't mean the agency will be working with a tightening pool of information.

"I don't think of summary reporting as FDA getting less information about adverse events; rather, I think of it as FDA gaining more comprehensive information," she said. "Because when you get individual reports, sometimes there might be outstanding issues as to why they're considered to be MDRs – issues that are not necessarily related to the device itself.

"But getting that summary information, where the company has performed an evaluation of the data it has selected based on its device, gives the agency a better understanding of how that device is working in the real world, rather than looking at one-off individual reports," Gunawardhana added. "It helps FDA decide whether that product should still be in the marketplace, or whether FDA should issue some cautionary information to health-care providers or practitioners."

She said summary MDR reporting likely helped FDA spot a trend of problems related to improperly cleaned duodenoscopes and endoscopes that led to the deaths of at least 10 patients between 2013 and 2015.

"Having all of that information come into the agency – the summaries of, 'Hey, we've had so many events at so many different hospitals, and people have gotten sick from it,' allowed the agency to more quickly put out information that there was a serious health issue," Gunawardhana said.

> The Food and Drug Administration Amendments Act (FDAAA) instructed FDA to accept quarterly summary reports for certain devices, but the agency has flouted that requirement for 10 years.

FDAAA SUMMARY REPORTING IGNORED

But FDA seems to be of two minds when it comes to summary MDR reporting.

Long before MDUFA IV, the Food and Drug Administration Amendments Act of 2007 (FDAAA) instructed the agency to accept quarterly summary reports from makers of all class I devices, and class II products that aren't permanently implantable, life-supporting or life-sustaining.

Despite the low risk of the products fingered by FDAAA for summary reporting, the agency has flouted that requirement for 10 years with little explanation.

Issued Nov. 8, FDA's new industry guidance, "Medical Device Reporting for Manufacturers," makes clear that the agency has no plans to implement FDAAA's summary reporting mandate. "Pending further notice, [those] devices currently remain subject to individual reporting requirements under 21 CFR, Part 803 [the MDR regulation] in order to protect the public health," states the document, referring to class I and II products.

"FDA basically said, 'We think everything needs to still be reported on an individual basis, so we're just not going to do that.' And so, FDA hasn't done it. And FDA keeps saying, 'Oh, maybe we will in the future" – but the agency won't follow that FDAAA directive," attorney Jennifer Newberger of the law firm Hyman, Phelps & McNamara said in an interview.

"I think the fact that FDA hasn't done it yet shows that it's really afraid of not learning about a device problem that it thinks it needs to know about that would come through in an individual report," Newberger said.

Through its actions, FDA might be signaling for more individual and summary reporting.

"The agency wants to know about those individual reports, but it also wants to know what the firm found out after its investigation, based on the total sum of the thing, and basically what the company has done to mitigate the problem," Gunawardhana said.

"That's why it's twofold. The agency does want the individual reports, because individual reports, if they are grave enough, the agency will step in immediately and say, 'You need to do a recall. We don't want five people getting injured before you do something,'" she said. "For example, there are condoms that are in class II, and if you had a situation with a condom and there was some kind of outbreak, then yes, I can see why the agency would say, 'We need to have that information right away.'"

Gunawardhana pointed out that courts have always deferred to FDA when it comes to decisions about protecting public health.

"I don't think, even if FDA is in violation of the FDAAA, that any court would say, 'Hey, you guys made the wrong decision,'" she said.

"FDA is kind of flexing its regulatory muscle here and saying, 'We still want the individual reports because that could lead to a recall, and we want to know about it. But we also want the summaries, because the summaries give us a better idea of the problems that are associated with this device, and whether they've been mitigated or whether they've not been mitigated. And what we need to do as an agency is to put out an alert. We may need to ask the company to do a recall.'"

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Can A Device Remain On EU Market When Its Notified Body Ceases To Operate?

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An increasing number of EU notified bodies are ceasing operations or having their scope restricted in the medtech space due to either a lack of resources to manage the increasingly tight requirements, or because they have failed assessments and have been "denotified."

But what is happening to the products for which these notified bodies have granted certificates? Are they allowed to remain on the market? And who has responsibility while the companies seek another notified body to take on responsibility for those products? These are critical questions that more and more device manufacturers are facing.

From a regulatory point of view, the validity of EC certificates during such a transitional period has not been fully clarified. But it now seems that the at least some regulators – aware of the problem and its urgency – are supporting an approach that allows a grace period for manufacturers left orphaned by their notified body, unless particular circumstances offer a reason not to provide this flexibility.

This grace period, however, might undercut the EU movement to tighten control over medical devices, some say. Should products, which are CE-marked and which bear the number of the notified body that assessed them, be allowed to circulate with no notified-body backstop? Have the authorities enough resources to oversee this situation across the EU?

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A New Landscape

The question of what happens to products certified by a notified body that goes out of business has been a growing issue in recent years, as notified-body numbers have plummeted by some 25% – from a height of around 80 before the joint assessments of notified bodies by European regulatory authorities began, down to about 60 now, after 55 joint assessments have been conducted.

The recent disappearance of many notified bodies, and the reduction in scope of others, has resulted in approximately 3,000 EC certificates previously granted by a notified body currently not being monitored by a notified body.

Manufacturers are having trouble finding a new notified body on short notice to get their products certified – a process that currently may take up to one year to complete.

THE PRACTICAL SOLUTION

The practical grace-period approach is beginning to be adopted around Europe, and has been the subject of official statements by French and Swiss authorities. It is based on an internal guidance document "unanimously agreed" by the European Commission's Competent Authorities for Medical Devices (CAMD) group at its October meeting in Bratislava, Slovakia.

This guidance suggests that the authorities responsible for market surveillance may grant affected manufacturers a certain period (called the "period of grace" (PoG) in Europe), during which the marketing of safe and effective medical devices affected by the withdrawal of the designation will be tolerated and the manufacturer will be given the opportunity to restore conformity with the regulatory requirements.

The nonpublic CAMD document is not legally binding, *Medtech Insight* understands.

THE FRENCH RESPONSE

The French national agency for the safety of medicines and healthcare products (ANSM) was, it appears, the first authority to publish its procedure, describing the CAMD document as "in perfect keeping with ANSM's position."

In so doing, it acknowledges that there is currently no European regulation that includes specific provisions concerning the consequences of a notified body's denotification on manufacturers that relied on its services. It asks affected manufacturers to contact a new notified body as soon as possible to obtain new certificates quickly.

ANSM says that marketing of these orphaned products can continue until the end of the initial period of validity of the certificates, but up to a limit of 12 months following denotification, or the effective end of activities, of the notified body. Marketing, ANSM says, may continue as long as the manufacturer has a valid CE certificate for the product at the time of its application, and a date of validity subsequent to that of the denotification of the notified body.

The French authorities also require the manufacturer to provide:

- A list of the references for all devices and IVDs affected by the denotification or the end of operations; this list should also specify the sales volume and the EU member states where they are being marketed and/or distributed;
- A copy of the most recent version of the CE compliance certificates identifying the products covered by these certificates;
- A statement issued by the manufacturer certifying that its products continue to comply with fundamental requirements;
- Identification of the new notified body, evidence that the certification process has been initiated; and
- The anticipated date that it will be finalized.

Finally, the audit report drafted by the new notified body should be sent to ANSM as soon as possible, as well as the new certificate.

ANSM makes it clear that it will not grant an extension for the marketing of the medical devices where the manufacturers' certificates have expired at the time of the application period, or if the validity date does not fall after the date of the notified bodies' denotification. However, if a medical device is essential or has no existing alternative, ANSM will examine the manufacturer's application on an individual basis. In this particular situation, the agency says, it is the manufacturer's responsibility to provide evidence of the essential nature of the medical device.

> Manufacturers have to apply in each country to which they intend to ship devices and place them on their markets, TEAM-NB's Francoise Schlemmer says.

SWISS RESPONSE

In response to multiple requests to the Swissmedic agency, the Swiss – who are not EU members but have a Mutual Recognition Agreement with the EU in the medtech sector – have followed with an approach that is very close to the French.

And Bernhard Bichsel of Swissmedic told *Medtech Insight* that while he cannot speak for other authorities, "as far as I know, most authorities will act accordingly."

Swissmedic is giving manufacturers based in Switzerland a maximum of 12 months PoG following the partial or complete de-designation of their former NB to restore the legal conformity of their product.

During this period, Swissmedic says it will not take action against devices placed on the market bearing the identification number of the "old" NB provided certain conditions are met in full, and that certain documents are submitted.

Bichsel said the published procedure reflects Swissmedic's general approach in handling those EC certificates, whether the notified body that awarded the original certificate ceased operations due to its own volition or because it had failed an assessment. "However, as for all other nonconformities," Bichsel said, "each is treated case by case and based on our risk-based approach, which allows taking into consideration other possible risks as well, e.g. reasons for denotification."

Swissmedic's conditions include:

- The manufacturer must demonstrate that the process of renewing the EC certificates of the affected products has been started with a new NB; and
- That the manufacturer submits to Swissmedic within 30 days of its notified body being de-designated written confirmation that the above conditions are met in full, along with the following documents:
  - A copy of the EC certificate and any associated product lists;
  - The declaration of conformity for the products concerned;
  - Written confirmation from the new notified body that the process for issuing a new certificate has been started; and

- The planned timeline.

Swissmedic states that it is important to realize that the 12-month period is not an official extension of the validity of an EC certificate; "It is merely a period of time granted to a manufacturer, in consideration of the proportionality principle, to eliminate the formal deficits not caused by its own fault."

At no point, it says, does Swissmedic assume the obligations and responsibilities of a notified body; indeed, it confirms that the agency reserves the right at any time to take action against manufacturers whose products do not comply with the requirements or represent a risk and to order appropriate measures.

When it comes to issuing export certificates, Swissmedic says it will issue export certificates – such as free sale certificates – for affected EC certificates on application until the end of the PoG. The export certificates will be issued with the usual period of validity and in keeping with usual practice.

NOT ALL OF EU

Speaking on behalf of the EU notified bodies association, director Francoise Schlemmer said that TEAM-NB is not aware of any harmonized approach.

The German authority has said that there was a "sort" of agreement, she told *Medtech Insight*. Schlemmer added that the French procedure is only applicable to companies with a headquarters in France. "Germany is working on a procedure for Germany, similar to the one in France, but for Germany."

At the moment, she explained, manufacturers have to apply in each country to which they intend to ship devices and place them on their markets. One application in country will most likely only cover a single country.

"We do not believe that one member state will accept the decision of another member state," Schlemmer said.

In the UK there is no specific "period of grace" for companies whose notified body is de-designated, the discussions with the MHRA are primarily based around using the existing transfer process for certifying new clients with no specific dispensation given. If anything the MHRA are expecting greater scrutiny in this situation as the assumption is that the previous reviews, particularly technical file reviews will not be to the required standard."

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3D Printing Opens A Legal Brave New World

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As 3D printing gets off the ground as a medical device manufacturing tool, attorneys are exploring the many legal issues that may arise from the practice. A new white paper from law firm Reed Smith attempts to address major legal issues raised by 3D printing of devices, pointing to many uncertainties that have yet to be tested in the courts.

"While the technology is still in its infancy and the law is untested in many respects, understanding the legal issues is the first step to avoiding potential pitfalls for anyone associated with 3D printing, from designers, to manufactures, to sellers, to consumers," the attorneys emphasize.

The authors urge all parties to commercial contracts in the 3D medical device printing sector to reevaluate the choice of laws they rely on, intellectual property, tax, confidentiality, indemnification, covenants and quality standards, representations and warranties, and insurance provisions. Maybe two of the most important topics for manufacturers in the document, product liabilities and intellectual property, were coauthored by attorney Matthew Jacobson.

"As 3D printing becomes more commonplace, it is only a matter of time before courts are faced with the quandary of whether traditional tort liability principles will apply to 3D-printed products and manufacturing techniques, or whether new laws will need to be created," he and his coauthor write in the document.

Jacobson spoke to *Medtech Insight* about why the white paper is important for stakeholders of device 3D printing, especially since so much is still untested.

"Just being aware that the law will likely change – maybe not tomorrow, but will likely change in the next few years – is important so that everyone can protect themselves from potential liabilities, as well as understand what their rights are," he said in the interview.

Jacobson and his coauthors say that since traditional product liability is tied to manufacturing function, it is "ill-suited" to help resolve legal issues when they involve nontraditional manufacturers such as 3D-printing stores, public libraries and hospitals. On top of that, they note that things become even more complicated when US FDA steps in to regulate the industry. The agency has been moving quickly to be more engaged with recently held workshops, and has released a draft guidance on the issue and created a new webpage that is expected to be a resource of aggregated information for sponsors.

But FDA has still not tackled issues such as bioprinting, printing of human cells and tissue, and point-of-care manufacturing. The authors expect more guidances and regulations as new products using such technology make their way through FDA's regulatory process.

TORT LAW EVOLUTION

One key issue will be how tort law evolves in this area. Johnson and his coauthors say understanding what tort law is in place and what may be coming is crucial for all involved.

"Understanding the relevant issues and anticipating the future of tort law should

be of interest not only to traditional and untraditional 3D-printing manufacturers, but also to those who manufacture and sell 3D printers, the internet file-sharer, the 3D-printing service provider, the raw-materials supplier, the 3D-printing hobbyist, and even the end user," they state in the white paper.

"3D printing brings many never-before-seen possibilities. It also brings a lot of unknowns. Understanding the tort liability unknowns and possible consequences is important to anyone who is interested or who is already involved in 3D printing," writes Jacobson and his coauthor.

An understanding of the legal issues is the first step, and maybe most crucial, to being able to anticipate the changes in the law and protecting yourself from liability."

They add that 3D printing will continue to disrupt tort law and it will likely take decades for the legal system to fully address the various legal nuances of the technology.

Jacobson and his colleagues are also concerned that 3D printing can be disruptive to traditional intellectual property rights. They note that the patents behind 3D printers have expired and now anyone has the ability to produce their own printers, and there is a high risk of pirating devices either by stealing product designs or reverse-engineering them. The big issues now are not about patents, but copyrights.

"With 3D printers ... you can take any existing object, scan it, create an electronic file and then 3D-print that product," warned Jacobson. "By doing so, you could take someone's copyright or logo off the product and claim it as your own, which goes against copyright law, and in the future will cause numerous products to be in violation of copyright laws."

He says it's important for manufacturers to understand how their copyrights may be violated so they can think of ways to prevent or at least mitigate those problems in the future.

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FDA Moves Mesh Surgical Instrumentation Up To Class II In Final Order

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In a Jan. 6 final order moving surgical mesh instrumentation for women undergoing pelvic organ prolapse (POP) or female stress incontinence from class I to class II, US FDA said adverse events associated with the procedures demands upgraded classification and special controls for the devices.

"FDA determined that perioperative adverse events occur during all types of urogynecologic surgical mesh procedures to treat female SUI and POP," the final order states. Among the adverse events associated with use of the instruments were organ perforation and injury, vascular injury and bleeding, and nerve injury and pain, the agency noted.

FDA cited the following rates of adverse events seen in POP and SUI procedures:

- **Vascular injury and bleeding:** Rate varied between 0.4-29.4% in studies describing retropubic SUI procedures; 0.2-11.9% in studies describing transobturator SUI procedures; 1-20.5% in studies describing mini-sling SUI procedures; 0.7-7.7% in studies describing transvaginal POP repair procedures; and 2.8% for one study describing sacrocolpoplexy procedures.
- **Organ perforation and injury:** Rate varied between 0.3-23.8% for retropubic SUI procedures; 0.2-5.8% for transobturator SUI procedures; 0.2-2.6% for mini-sling SUI procedures; 0.7-13.1% for transvaginal POP repair procedures; and 3.6% for one study describing sacrocolpoplexy procedures.
- **Nerve injury and pain:** Rate varied between 0.1-5.3% for retropubic SUI procedures; 0.8-30.8% for transobturator SUI procedures; 1.1-4.1% for mini-sling SUI procedures; 6.0-39.1% for transvaginal POP repair procedures; and 14.9% for sacrocolpoplexy procedures.

The agency also modified some of the special controls it will apply to the surgical mesh instrumentation in its final order from what it suggested in a proposed order issued in May 2014. First, FDA is requiring a demonstration that the devices, if reused, can be adequately reprocessed to remove contaminants. Second, the agency is revising its proposed special controls by mandating that nonclinical performance testing demonstrate the instruments meet all design specifications, and that they perform as intended under anticipated conditions-of-use.

ADVISORY PANEL EMPHASIZED GOOD TRAINING

At a February 2016 meeting, FDA's Gastroenterology-Urology Devices Panel unanimously endorsed the agency's proposed plan to up-classify the instruments, agreeing that they can pose a series of risks to women, but also emphasized that the instruments need to be used by experienced and highly trained gynecological and urological surgeons.

Panel members noted that recent iterations of surgical mesh instruments have been smaller, with sharper tips than past models, rendering them more apt to pierce organs, particularly when used by inexperienced surgeons.

Among the special controls supported by the both the panel and FDA for use of the surgical mesh instruments were biocompatibility with human tissue, ability to be made sterile, and better labeling.

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Bone Anchor 510(k) Guidance Gets Update

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US FDA's recommendations on pre-market submissions for bone-anchor devices got a facelift for the first time since 1996 via a Jan. 3 draft guidance document.

The device center had promised the revisions on its list of planned guidances for 2016 as part of FDA's ongoing retrospective review process for documents that haven't been updated in at least a decade. The bone anchors addressed by the guidance are classified under 21 CFR 888.3030 and 21 CFR 888.3040, and are used to secure soft tissue to bone.

The revised guidance offers detailed recommendations for clinical and non-clinical testing. Specifically, non-clinical testing should address suture characterization, corrosion for metallic bone anchor materials, fatigue and degradation. In addition, nonclinical testing should be used to check the bone anchor's safety during insertion, pullout and component interconnection. Clinical testing isn't needed for most bone anchors, but reviewers may ask for it in certain situations, such as if the indications for use or technology differ from that of predicate devices.

The guidance says device descriptions within 510(k)s for general suture anchors should include the bone anchor's dimension and material. FDA recommends the discussion of dimensions include fully dimensioned engineering drawings for each device component. If the bone anchor uses multiple components, the 510(k) should describe how the components are assembled; if it ships with a suture, manufacturers should provide the identity and materials of the sutures, as well as the suture size under the US Pharmacopeia system. If the anchor as shipped doesn't include a suture, manufacturers should explain what sutures it should be used with.

Meanwhile, descriptions of nitinol suture anchors should describe how the device conforms to applicable material standards, or include the chemical composition if none apply. The 510(k) should include the transition temperatures of the final, finished device, as well as a description of the final processing. And descriptions of polymeric absorbable sutures should identify the material and applicable consensus standards, as well as a description of the as-manufactured analytical properties of the device and an explanation of the degradation process and timeframe. If the materials of a polymeric absorbable suture do not match that of the predicate device, and the manufacturer is relying on a risk assessment to address biocompatibility concerns, the 510(k) should include specifications for the raw material and a description of the processing used to create the final device.

> FDA wants manufacturers to conduct a biocompatibility risk assessment if there is no predicate device using the same materials with a similar location and duration of use.

For all types of bone anchors, the 510(k) should include a seven-point comparison between the new device and the predicate device that addresses such points as anchor geometry, anchor material and range of suture diameter.

If there is no predicate device using the same materials with a similar location and duration of use, FDA wants manufacturers to conduct a biocompatibility risk assessment. This should address endpoints including cytotoxicity, sensitization, genotoxicity and carcinogenicity. And any coating used in suture components should be evaluated for biocompatibility, as should the main suture material. In addition, biocompatibility testing of degradable anchors should look at the risk factor over the life of the device.

FDA expects to see a range of other issues addressed in bone-anchor 510(k)s, including sterility, reprocessing, pyrogenicity, shelf life and packaging. For most of these topics, the draft guidance suggests manufacturers rely on previous FDA guidances and applicable international medical device standards.

The draft guidance also addresses when FDA would want to see a new 510(k) after a device modification. One would be expected if the manufacturers makes the suture or anchor smaller or larger, modifies the insertion technique, or modifies the material – for example, going from a non-absorbable to an absorbable suture. Each of those things "could significantly affect the safety and effectiveness of the device," FDA says.

However, the agency won't want a new 510(k) if a manufacturer adds a suture of identical design but an intermediate length (for example, adding a 15mm suture length to a product line that already includes 10mm and 20mm lengths) or increases the length of the suture inserter handle.

The agency is collecting comments on the draft guidance through March 6 under docket No. FDA-2016-D-4436.

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Abbott Becomes CRM Player Overnight

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Abbott Laboratories Inc.'s acquisition of **St. Jude Medical Inc.** gives it the second biggest share of the cardiac rhythm management device market, a space it has not competed in before.

The acquisition, worth $25b, was first announced in April, closed Jan. 4. It cleared the final hurdle in late December when the US Federal Trade Commission approved the deal on the condition that Abbott sell St. Jude's vascular closure device business and Abbott's steerable sheath for cardiac ablation catheters to maintain competition in the market for those types of devices.

Medical devices are already the slowest growing of Abbott's four main product divisions – medical devices, drugs, diagnostics, and nutrition – and the addition of St. Jude's portfolio is not likely to change that soon. For the third-quarter of 2016, the last quarter St. Jude reporting earnings, the company's total revenue grew 2% year-over-year on a comparable, constant-currency basis.

However, Abbott believes adding St. Jude's complimentary product portfolio will improve the combined company's leverage with cardiology device customers, who are increasingly looking to work with larger companies with broad product offerings rather than many different suppliers. When the deal was announced in April, Abbott touted the potential to enhance its global scale, infrastructure and capabilities, and in the release announcing the deal closed Jan. 5, Abbott says "this leading combined portfolio will have the depth, breadth, scale and innovation to help patients restore their health, improve outcomes and deliver greater value to customers and payors."

FROM NOTHING TO NUMBER TWO IN CRM

An example of an area where St. Jude could help Abbott's existing businesses is interventional cardiology. Abbott competes with **Medtronic PLC** and **Boston Scientific Corp.** in interventional cardiology with products like its *Xience* everolimus-eluting stent and the *Absorb* bioresorbable vascular scaffold. But, until now, Abbott was at a disadvantage versus those companies when trying to sell to customers looking for a broad cardiovascular device portfolio, because it did not provide any cardiac rhythm management devices.

While the addition of St. Jude's products will help existing Abbott device businesses, the resources and reach of Abbott may help St. Jude, especially in cardiac rhythm management, a market that has been growing slowly in the US and Europe.

According to a new market report from *Meddevicetracker*, the pacemaker market is expected to grow 6% on an annualized compound basis through 2021, but only grow 2.3% in the US and 3.7% in Europe as the intense competition in the space drives down prices. Meanwhile, the global implantable cardioverter defibrillator market is expected to grow just 3.7% annually and the resynchronization therapy (CRT) device market is projected to grow 5.3%, lead mostly by growth in Japan and emerging markets.

As the CRM market overall has matured and growth has slowed, St. Jude's share of the CRM market has been slipping, especially in the US, because of competition with Medtronic's line of CRM devices that are compatible with magnetic resonance imaging – a feature that has turned out to be an important product differentiator in the pacemaker, ICD, and CRT markets. During its third-quarter earnings call in October, St. Jude said it expects to earn FDA approval for MRI-compatible pacemakers by early 2017 and FDA-approval for an MRI-compatible ICD within the first half of 2017.

St. Jude's Q3 2016 revenue from "traditional" cardiac rhythm management devices – pacemakers and ICDs but not CRT devices – declined 7% year-over-year on a comparable basis, including a 17% drop in the US. For the quarter, revenue for St. Jude's Heart Failure division – which includes CRT devices, ventricular assist devices, and St. Jude's *CardioMems* heart failure monitor – were down 3% year-over-year, despite 10% growth in global VAD sales due to weakness in CRT sales caused by the same problems hindering its other cardiac rhythm management devices, according to the company.

Despite these struggles, St. Jude gives Abbott a strong presence in the CRM market as it is one of the only three major players. Meddevicetracker's report shows that St. Jude has around a quarter of the global market share in each of the three major categories of cardiac rhythm management devices – well behind **Medtronic PLC**, but ahead of **Boston Scientific Corp.** All the other players, including **Biotronik SE & Co. KG** and **LivaNova PLC**, have a combined global market share smaller than Boston Scientific's.

Based on full-year data from 2015, St. Jude Medical was the second largest supplier of pacemaker products to the global market with 24.1% of the market and $799.9m in sales while Medtronic was the global leader with an estimated market share of 50.4% and sales of $1.674.4m. Boston Scientific came in a distant third in the pacemaker market with 12% of the market and revenues of $399.9m.

All three major pacemaker companies are looking to a new generation of less-invasive, "leadless" pacemakers to drive growth in the market. St. Jude is developing a leadless pacemaker called *Nanostim*, but it is well behind Medtronic's *Micra* leadless pacemaker, which already has FDA approval. Boston Scientific is developing the *Empower* leadless pacemaker to go along with its *Emblem S-ICD* leadless ICD. ([A#MT104025])

In the global implantable cardioverter defibrillator market segment, St. Jude's market share was 25.9% with revenue of $1,170.0m while Medtronic had 40.7% of the market with sales of $1.843.2m. Boston Scientific was close behind St. Jude with $1,062.7 in ICD revenues and an estimated 23.5% market share. All other ICD players accounted for just around 10% of the total market.

St. Jude also has 23% of the cardiac resynchronization therapy (CRT) device market segment, with $530m in CRT revenues, well behind Medtronic, which owns nearly half the CRT market, but well ahead of Boston Scientific, which has 14.6% of the market, and all other competitors combined hold just 12.9% of the global CRT market.

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Court Revives Medtronic Stock Fraud Case

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A lawsuit alleging **Medtronic PLC** misled investors about risks posed by one of the company's products is back on, thanks to a ruling by a three-judge appeals court panel that sends the case back to a lower court.

Three pension funds, led by the West Virginia Pipe Trades Health and Welfare Fund, sued Medtronic in 2013 for securities fraud concerning the company's promotion of its *Infuse* biologic-based spinal bone-growth device. The Dec. 28 decision by the Eighth Circuit Court of Appeals throws out a lower court ruling that found the plaintiffs filed after the statute of limitations expired.

The suit alleges that Medtronic and its executives worked with several physician researchers to hide risks posed by Infuse's off-label use, which reportedly made up as much as 85% of its sales.

Medtronic said the suit should have been filed within two years of a May 2011 article that raised some concerns about Infuse's safety when used off-label. However, the appeals court countered that there wasn't enough information available at that time for a lawsuit to survive.

"Appellants could not have discovered with reasonable diligence sufficient information to plead scienter with the particularity necessary to survive a motion to dismiss prior to June 27, 2011. Appellants brought their complaint within the two-year statute of limitations," wrote Judge Raymond Gruender.

The court also disagreed with Medtronic's contention that previous case law established the plaintiff's liability claims were not valid. The plaintiffs "allege conduct beyond mere misrepresentations or omissions," Gruender wrote, noting that Medtronic reportedly worked with physicians to deceive the market.

A Minneapolis firefighters' pension fund brought the first securities fraud suit against Medtronic in 2008, alleging the company's off-label promotion of Infuse violated securities law. Medtronic agreed to make payments to the pension plan's participants in 2015.

"We're disappointed with the decision, but continue to believe the claims in this case are without merit," Medtronic spokesman Eric Epperson said. "The plaintiffs are still a long way from proving liability in this case, and we are prepared to defend ourselves in court."

Infuse has been at the center of several controversies over its safety and effectiveness. A 2013 analysis of clinical data found that the treatment offered little advantage over bone grafts, and in 2011 researchers learned that Infuse had a real adverse event rate of up to ten times that shown in published studies. Reviews have also found that Medtronic played an inappropriately large role in crafting published clinical trials. And in April 2016, the *Minneapolis Star-Tribune* alleged the company hadn't properly reported known adverse events to FDA – a charge Medtronic disputes.

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Philips, Illumina Sign Genomics For Cancer Pact

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Philips Healthcare and **Illumina Inc.** are collaborating to combine their respective know-how in cloud-enabled data management and next-generation sequencing to develop an integrated solution that brings together genomic and other data from myriad sources that will allow a deeper understanding of cancer cases and ultimately better management of cancer patients.

The jointly developed solution will incorporate Illumina's BaseSpace Sequence Hub, which connects the company's next-gen sequencing instruments and collects data from these data. The data will then be processed through Philips' IntelliSpace Genomics platform for oncology and added to other data from multiple sources – including radiology, immunohistochemistry, digital pathology, medical records and lab tests – and will deliver a consolidated dashboard view. The system will be for research only, helping to develop insights more efficiently and will ultimately support lowering the cost of health-care delivery and improved health outcomes, said the two companies.

Philips and Illumina added that they will also be looking for clinical research collaboration opportunities with US health systems that want to develop precision medicine programs in oncology.

Next-generation DNA sequencing is increasingly being used to genetically profile tumors. However, challenges remain in developing ways to rapidly and accurately interpret genomic findings in the context of a patient's condition, according to the two firms. While cancer patients can have hundreds of gene variants in their tumors, only a small number may actually drive the individual's specific cancer or may have actionable therapeutic implications for a particular patient. The patient's history, related lab tests and cancer-type are needed for a meaningful interpretation of the genomic data.

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STARTS & STOPS:

S-ICD And Respiratory App Studies Among Year-End Large-Scale Trial Launches

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Many like to end the year with a bang, and this seems to be the case even in the world of clinical trials. December's select list of trial launches, as recorded by *Meddevicetracker*, highlighted a number of studies expecting to enroll patients in the hundreds and the thousands.

Among these is Boston Scientific's 1,800-patient US IDE study, MADIT-ICD, to assess whether patients with prior myocardial infarction, diabetes and a relatively preserved ejection fraction of 36-50% would benefit from receiving a subcutaneous implantable cardioverter defibrillator system, compared to conventional medical therapy. Boston Scientific is collaborating with the University of Rochester for this study and is expected to complete it by March 2022.

Another sizeable study is from Australian digital health-care start-up, ResApp Health. The firm is looking to recruit 1,111 pediatric patients for its Smartcough-C trial to evaluate its *ResAppDx* mobile software app for diagnosing childhood pneumonia and other respiratory conditions. Collaborating with ResApp on the study are the Cleveland Clinic, Texas Children's Hospital and Massachusetts General Hospital. ResApp expects to complete the study by June this year.

Neurovascular technology specialist Penumbra initiated a Phase IV study of its *Smart* coil system for treating intracranial aneurysms and other malformations. The firm is expecting to enroll 1,000 patients and complete by August 2019.

The table below provides details of these and other trial initiations and completions reported between Dec. 5, 2016, and Jan. 3, 2017.

Information in this table is based on data from *Meddevicetracker*, which provides an interactive real-time analysis of device markets, companies and products, allowing you to quickly find the information and analysis you need to make strategic business decisions. For more information on the research covered in this article, click here.

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Trial starts and stops, Dec. 5, 2016 – Jan. 3, 2017

DATE	COMPANY	PRODUCT NAME	TRIAL NAME	COMMENTS
TRIALS INITIATED				
Jan 3, 2017	Cohera Medical Inc.	*Sylys* for Surgical Tools (General)	IDE - Ileorectal Anastomosis + Sylys (US)	A randomized clinical trial to compare patients undergoing colorectal and ileorectal anastomosis after resection with and without the Sylys surgical sealant. The study is the first phase of a clinical trial program designed to support the safety and efficacy of the sealant in reducing the leak rate in these procedures. It expects to enroll around 750 patients.
Jan 3, 2017	Bonus BioGroup Ltd. (TLV:BONS)	*BonoFill* for Bone Fractures and Mechanical Defects	Phase I/II - CP-BNS-03 (Israel)	A Phase I/II, open-label, first-in-human, single-center clinical study aimed to evaluate the safety and efficacy of BonoFill-II in reconstructing maxillofacial bone. It expects to enroll 20 patients.
Dec 29, 2016	BioCardia Inc. (BCDA)	*CardiAMP* Companion Diagnostic for Congestive Heart Failure (CHF) and Cardiomyopathies	IDE - CardiAMP Heart Failure Trial	A randomized, controlled, trial of up to 260 patients evaluating CardiAMP cell therapy at up to 40 clinical sites in the US.
Dec 19, 2016	Micro Interventional Devices Inc.	*MIA* for Cardiac Valve Surgery	STTAR (EU)	STTAR (the Study of Transcatheter Tricuspid Annular Repair) is an EU multicenter safety and performance study of the MIA technology, designed for minimally invasive tricupsid and mitral repair.
Dec 19, 2016	Endonovo Therapeutics Inc. (ENDV)	*Immunotronics* for Congestive Heart Failure (CHF) and Cardiomyopathies	Preclinical study	The study will assess the therapeutic potential of the Immunotronics platform in the prevention of heart failure following myocardial infarction (MI). It will evaluate the effect of the noninvasive electroceutical technology on cardiac function, post-MI remodeling, and infarct size, as well as angiogenesis.

DATE	COMPANY	PRODUCT NAME	TRIAL NAME	COMMENTS
Dec 15, 2016	Koninklijke Philips N.V. (PHG)	*SyncVision* for Coronary Artery Disease	Prepare II (EU)	A prospective, single-arm, open-label, user evaluation study of the SyncVision System with software v4.X. It expects to enroll 200 patients.
Dec 15, 2016	Aethlon Medical Inc. (AEMD)	*Hemopurifier* for Antiviral – Other Treatments	Sepsis-Related Virus Study	A research study to validate the ability of the Aethlon Hemopurifier to capture viruses that are associated with increased mortality in immune-suppressed sepsis patients. The study is designed to validate the *in vitro* capture of Cytomegalovirus (CMV), Epstein-Barr virus (EBV) and Herpes Simplex Viruses (HSV). Upon successful completion, Aethlon will seek to demonstrate that the Hemopurifier can simultaneously capture all three viruses.
Dec 13, 2016	Boston Scientific Corp. (BSX)	*S-ICD System* for Ventricular Tachycardia or Fibrillation	IDE - MADIT S-ICD (US)	A study of up to 1,800 patients to evaluate if subjects with a prior myocardial infarction, diabetes mellitus and a relatively preserved ejection fraction of 36-50% will have a survival benefit from receiving a subcutaneous implantable cardioverter defibrillator (S-ICD) when compared to those receiving conventional medical therapy.
Dec 13, 2016	INSIGHTEC Ltd.	*ExAblate System* for Alzheimer's Disease (AD)	Phase I/II - BBB-Alzheimers (CAN)	A Phase I/II prospective, non-randomized, single-arm, feasibility study to evaluate the safety and initial effectiveness of opening of the Blood-Brain Barrier with intravenous contrast agents using the ExAblate Neuro System in patients with early stage Alzheimer's Disease. It expects enroll six patients.
Dec 11, 2016	Koninklijke Philips N.V. (PHG)	*Microdose Si* for Breast Cancer - Imaging	DOC-EMOA-A7UDZ2 (EU)	A study to evaluate image quality of a low-dose tomosynthesis system versus a comparator. It expects to enroll 60 patients.
Dec 9, 2016	ResApp Health Ltd. (ASX:RAP)	*ResAppDx* for Respiratory Disease	SMARTCOUGH-C (US)	A prospective, double-blind, multisite clinical study to evaluate the ResAppDx mobile software app for the diagnosis of childhood pneumonia and other respiratory conditions. It is expected to recruit up to 1,111 patients between the ages of 29 weeks and 12 years.
Dec 6, 2016	Penumbra Inc. (PEN)	Penumbra *SMART COIL* for Aneurysm	Phase IV - SMART (US)	A Phase IV, prospective, multicenter study to gather post-market data on the Penumbra SMART Coil System in the treatment of intracranial aneurysms and other malformations. It is expecting to enroll a thousand patients.
Dec 6, 2016	Axonics Modulation Technologies Inc.	Axonics *SNM System* for Fecal Incontinence Treatment	Fecal Incontinence Study (EU)	A study to evaluate the performance of the Axonics SNM system as a treatment for the symptoms of fecal incontinence. Twelve patients are expected to enroll. The system is CE-marked and has demonstrated efficacy in treating symptoms of overactive bladder.
Dec 5, 2016	BIOTRONIK AG	*BioMonitor* for Atrial Fibrillation/ Flutter	BioInsight (US)	A multicenter, prospective, nonrandomized post-market study. Up to 75 participants anticipated; the study will evaluate the safety and feasibility of performing the minimally invasive BioMonitor 2 insertion procedure in an office setting.
TRIALS SUSPENDED				
Dec 22, 2016	SomnoMed Limited (SOM:AU)	*SomnoDent* for Sleep Apnea	MAD Effectiveness Study (Belgium)	A prospective evaluation of the overall effectiveness, including cardiovascular effectiveness, of the custom-made, titratable duoblock flex SomnoDent MAS (mandibular advancement device) in the treatment of obstructive sleep apnea. The study was initiated in November 2014 and was expecting to enroll 50 patients. However, as of Dec 2016, the recruitment status is unknown and the status has not been verified for more than two years. Given this information, the company is suspending this trial.

DATE	COMPANY	PRODUCT NAME	TRIAL NAME	COMMENTS
TRIALS COMPLETED				
Jan 3, 2017	Bonus BioGroup Ltd. (TLV:BONS)	*BonoFill* for Bone Fractures and Mechanical Defects	Phase I/II - CP-BNS-02 (Israel)	A 20-patient Phase I/II, open-label, first-in-human, single-center study aimed to evaluate the safety and efficacy of BonoFill in reconstructing the bone.
Jan 3, 2017	Stryker Corporation (SYK)	*LFIT* Anatomic Femoral Heads with X3 Liners for Cartilage and Joint Repair	LFIT (US)	An open-label, prospective, post-market, multi-center clinical evaluation of the LFIT Anatomic CoCr Femoral Heads with X3 Inserts. Ninety-six patients were enrolled.
Dec 21, 2016	Medtentia International Ltd. Oy	Medtentia *Helix Ring* for Cardiac Valve Surgery	Study 2010-040 (Safety/ Performance; Finland)	A study to evaluate the Medtentia annuloplasty ring in improving mitral regurgitation. It was initiated in 2012 and expected to enroll 230 patients. It only enrolled 12 patients, but Mententia announced in October 2016 that it completed the analysis of the results from the proof-of-concept study, and the main safety and performance objectives were achieved.
Dec 18, 2016	Bigfoot Biomedical Inc.	Bigfoot *smartloop* for Diabetes Mellitus, Type I	IDE - TST-10025 (US)	A 20-patient Phase I trial designed to assess safety and feasibility of the Bigfoot Biomedical Type I Diabetes Management System (T1DMS) in up to 50 participants in a closely monitored Clinical Research Center (CRC) environment.
Dec 18, 2016	Silk Road Medical Inc.	*ENROUTE NPS* for Embolic Stroke Prevention	Phase III - ROADSTER	A 286-patient, Phase III study to evaluate the safety and effectiveness of the MICHI Neuroprotection System with Filter (Enroute) in providing cerebral embolic protection during carotid artery stenting (ROADSTER Study).
Dec 18, 2016	Bellerophon Therapeutics Inc. (BLPH)	Bioabsorbable Cardiac Matrix (BCM) for Congestive Heart Failure (CHF) and Cardiomyopathies	Phase II - PRESERVATION I	A Phase II study to evaluate the safety and effectiveness of the IK-5001 device for the prevention of ventricular remodeling and congestive heart failure when administered to subjects who had successful percutaneous coronary intervention with stent placement after ST segment elevation MI (STEMI). A total of 306 patients were recruited.
Dec 14, 2016	Geistlich Pharma AG	*Chondro-Gide* for Cartilage and Joint Repair	Phase III - 10830-003 (Germany)	A Phase III study to evaluate the safety and effectiveness of using Chondro-Gide collagen membrane either sutured or glued compared to microfracture alone in the treatment of symptomatic cartilage defects of the knee. Sixty-seven patients were recruited.
Dec 13, 2016	Bayer AG (BAYRY)	*Essure* for Contraception	SUCCES II (FRA)	A 2,644-patient study using a survery to confirm the effectiveness of the Essure method, and to obtain more information on the conditions of use as well as on the methods used during the three-month checkup, as well as the 12-month, 24-month and five-year follow-up on patients.
Dec 8, 2016	Abbott Laboratories (ABT)	*ABSORB BVS* for Coronary Artery Disease	ASSURE (Germany)	A registry, with 183 patients, to evaluate the safety, performance and efficacy of the Everolimus-eluting bioresorbable vascular scaffold (BVS) system in patients with *de novo* native coronary artery lesions in all-day clinical practice.
Dec 6, 2016	Cefaly Technology	*Cefaly* for Migraine and Other Headaches	Phase II/III - ANODECCH (University Hospital of Liege; EU)	A 32-patient, Phase II/III pilot study of anodal transcranial direct stimulation (tDCS) of the anterior cingulate gyrus for the treatment of episodic and chronic cluster headache.
Dec 5, 2016	Johnson & Johnson (JNJ)	*DERMABOND* for Wound Healing	Study 774875 - UC Davis (US)	A 50-patient study to determine whether the use of 2-octylcyanoacrylate (Dermabond) during repair of linear cutaneous surgery wounds improves scar cosmesis compared to wound closure with 5-0 fast absorbing gut.

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