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WARNING LETTER NOSEDIVE:

US FDA Writes Fewest Quality-Related Missives Since 2002; Agency Isn't Sure Why

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Medical device manufacturers racked up a mere 57 quality-related warning letters in 2016 – a 14-year-low that has left US FDA scratching its head as to why so few were sent to firms.

Last year's count, shared by FDA with *MedtechInsight*, is 64 fewer than in 2015, when 121 quality system letters were released – a 53% decrease. Twenty-two were sent to US firms; 35 to foreign ones. (See infographic, p. 21.)

2016's 57 letters represents the second-lowest number recorded since the Quality System Regulation came into force in 1996. The only year when there were fewer letters was 2002, when 42 were written by the agency, FDA data shows.

FDA considers quality-related letters to be those that only include an alleged violation of the QSR. In its count, it does not include letters that solely pertain to the Medical Device Reporting (MDR) regulation (21 CFR, Part 803) or the Corrections and Removals regulation (21 CFR, Part 806), or pre-market activities. (There were eight warning letters that fit this bill in 2016, for a grand total of 65 missives to industry last year.)

"Compliance reached out to CDRH and Office of Regulatory Affairs staff to try to identify factors, broadly, that would account for the warning letter decline," but no explanation could be found, said Sean Boyd, deputy director of the Office of Compliance within FDA's device center.

The Office of Regulatory Affairs – ORA – conducts all of the agency's field activities.

Boyd's compliance group also "looked at the total number of inspections – foreign and domestic – and, generally, we did not find any particularly compelling reasons that accounted for the 2016 decline."

In an interview with *Medtech Insight*, Boyd provided two examples of ongoing initiatives that were reviewed to determine if they had any impact on the dip in warning letters: recent benefit-risk activities at the agency and in industry, and the joint FDA/Medical Device Innovation Consortium (MDIC) Case for Quality. But those initiatives couldn't explain the decrease in missives, either.

"In the case of benefit-risk, for example, [FDA's] guidance was published late last year. While the guidance formalizes approaches taken to consider benefit and risk, we haven't taken steps to really dramatically change the way we make

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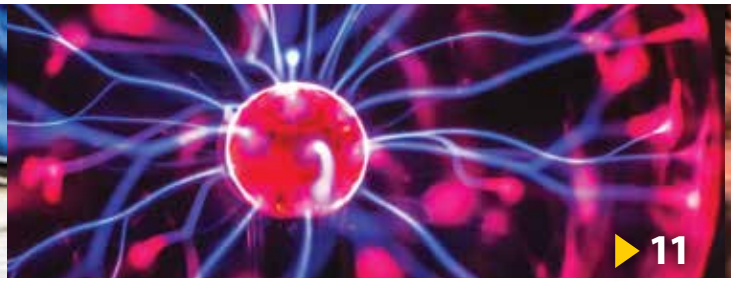
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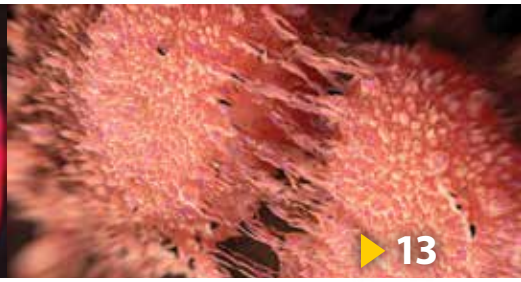
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Medtech insight

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procedures, the National Institute for Health and Care Excellence concludes in a new guidance.

11 **Infusion-Pump Maker Ivenix Closes Initial Tranche Of $50m Financing –** Ivenix Inc. said it has closed on the first tranche of $50m in equity financing, which will put the Amesbury, Massachusetts-based infusion-pump startup on track to pursue FDA approval for its *Ivenix Infusion System*.

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19 **Former Siemens CMO Tapped To Run US Health IT Policy –** Donald Rucker, who spent 13 years as chief medical officer of Siemens Healthcare, has been tapped as the US National Coordinator of Health IT, according to a government directory listing.

US FDA's 'Program Alignment' Inspection Scheme Coming Mid-May; Details Still Murky

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Mark your calendar: US FDA investigators will begin inspecting device manufacturing facilities using the agency's brand-new "program alignment" inspectional approach on May 15.

That's according to Robin Newman, director of the Office of Compliance within FDA's Center for Devices and Radiological Health, who says agency staff is "working very hard" to make sure the scheme is ready for primetime on that date.

"There are a lot of moving parts, and it's an unenviable thing to try to do. But at the same time, I think it's really going to benefit everyone," Newman said March 27 at FDAnews' 14th Annual Medical Device Quality Congress in Bethesda, Md.

Under program alignment, facility inspections performed by the Office of Regulatory Affairs (ORA) will be structured along commodity-specific product lines – a historic change for the office, which conducts all of the agency's field activities. One of the plan's goals is to make inspections more predictable and consistent for investigators and manufacturers.

The change means a majority of firms will likely be exposed to an entirely new, unfamiliar inspectorate, among other big changes.

"With program alignment, you're going to get investigators and managers, and specialists by program. You're going to get an increased understanding of [device] technology because they are specialists," Newman said.

"And I suspect you will also see over time some sub-specialization within this group as well," she added, noting that the agency could use sterilization specialists, for example, if the need arises.

The inspection scheme calls for the agency's five regional offices to be replaced by three distinct districts within the US. *(Also see "Kiss Your FDA Regional Office Goodbye: Big Changes Afoot Thanks To ORA's Inspectional Program Alignment" - Medtech Insight, 21 Mar, 2016.)*

Further, Boston, Florida and Los Angeles will likely be home to new FDA divisions dedicated to coordinating inspections under the initiative, a longtime industry insider told *Medtech Insight* in a February podcast. *(Also see "Podcast: FDA's Inspection 'Program Alignment,' New Guidance Docs Top QA/RA Hotspots In 2017" - Medtech Insight, 1 Feb, 2017.)*

When pressed for details by *Medtech Insight* about how program alignment will be organized, Newman's lips were sealed.

"When you're dealing with a regulatory agency like FDA, you're dealing with unions, and until we have been given clearance to talk about what the plans are, we're not going to discuss them in public," she said. "We are kind of on a need-to-know basis only to some extent. We don't have a lot of information."

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In a recent Compliance 360° podcast, former FDA investigations branch director Ricki Chase said companies that make high-risk products or have risky manufacturing operations will likely be inspected more often under program alignment. *(Also see "Compliance 360° Part 7: Factors Feeding Your Inspection Cycle – A New Paradigm" - Medtech Insight, 20 Mar, 2017.)*

"When it is fully launched, [the scheme] will most likely have the most immediate, noticeable impact on inspectional frequency and exposure," said Chase, who is now compliance practice director for Lachman Consultant Services.

Program alignment will change how FDA selects companies to inspect, Chase said. "Much like the center for drugs, the center for devices is moving to a risk-based assessment of the medical device inventory. The assessment may include factors such as previous regulatory actions, time since the last inspection, [whether] the firm has never been inspected, serious recalls, numbers and types of complaints, new product to market, and indications from Medical Device Reports."

A risk score will be compiled by the agency, and firms with high scores might undergo more audits.

"Because the inspectional decisions will be based on risk and not on geographical distribution across districts, the personnel resources may be drawn from the national pool of all medical device investigators. In practicality, this may look like a firm with an inherently high-risk device or operation being subject to more frequent inspection regardless of compliance history," Chase said.

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Will EU's Delegated And Implementing Acts Replace Guidance?

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The European Commission has confirmed that it is empowered to adopt more than 80 delegated and implementing acts in the context of the EU's new Medical Devices Regulation (MDR) and the IVD Regulation (IVDR). The regulations are due to be finally adopted imminently and to take effect before the end of June.

At a stakeholder meeting organized by the European Commission and the Competent Authorities for Medical Devices (CAMD) group March 9, the Commission said that it considers 18 of these acts considered mandatory – meaning that they must be adopted within specified deadlines. But it has yet to confirm which ones.

The Commission's main priorities in terms of preparing relevant acts over the next few months, therefore, seem to generally reflect the earlier application dates of corresponding parts of provisions within the Regulations.

The good news is that the Commission seems to have assuaged any fears that EU decision-makers could use the acts to introduce controversial elements into the legislative framework without industry having its say. Under the EU's Better Regulation framework, there is normally a 4-week public feedback on proposed delegated and implementing acts.

Furthermore, there could be an impact assessment and a 12-week public consultation at an early stage of the process, when the content of the proposed acts is considered to be particularly sensitive.

Medtech Insight understands that shortly after the adoption of the Regulations the Commission should make available soon a list of acts that needing drafting.

WHERE DOES GUIDANCE FIT?

There has been much discussion about the type and quantity of guidance documents that are to be produced under the new regulations.

Much of the content that can be found within guidance documents that have been drafted over the years to support the current medical device directives has already been incorporated into the new regulations.

The MDR is 566 pages long, compared to the 60 pages in the Medical Devices Directive, and the IVDR is 477 pages long, compared to 37 pages in the current IVD Directive. Regulators explain the added heft of these documents by stating that they absorb the content of the prior guidance documents.

But due to the detail and complex of new regulations, there have been many calls for new guidance documents to explain some of the finer points of the new rules.

But at the European Commission's stakeholder implementation meeting earlier this month, the Commission clarified that guidance will only be adopted in areas which are not covered by the Commission's empowerment to adopt delegated and implementing acts.

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This adds to the urgency with which these acts – which must undergo a relatively lengthy formal process for adoption – need to be adopted.

GOVERNANCE AND STAKEHOLDERS

The European Commission also clarified at the meeting that the Medical Devices Coordination Group (MDCG) is to be established within six months of the regulations entering into force – likely by late November, or certainly by the end of the 2017.

It is intended to be an authorities-only group and to replace the current Medical Devices Expert Group – which comprises all relevant stakeholders, including industry, notified bodies and authorized representatives, in addition to the authorities.

The MDCG will be set as a Commission's expert group. While it will comprise authority-only representatives, its technical subgroups may include stakeholders, the Commission confirmed.

"The intention is to make sure that our current expert groups are carried over to the new regime, though in a more simplified and functional structure," explained Salvatore D'Acunto and Erik Hansson, respectively, the Commission's head and deputy head of the unit for health technology and cosmetics.

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Symetis TAVR Buy Not About Throwing Shade On Lotus, BSX Insists

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Boston Scientific Corp.'s Mar. 30 announcement that it was acquiring **Symetis SA**, a smaller European rival in the transcatheter aortic valve replacement market, was greeted with a good dose of skepticism. Some believe that the move is an indication of declining confidence by the US company in its own TAVR platform, *Lotus*, which was pulled off the shelves and out of ongoing clinical trials in February due to a reported defect.

Under the terms of agreement, Boston Scientific will pay $435m upfront, all-cash, for Symetis. The latter is considered a relative latecomer to the TAVR scene. Its *Acurate TA* device, which employs the transapical approach for implanting the aortic valve, was CE marked in 2011, but sales began to ramp up when the company launched its transfemoral *Acurate neo TF* system in 2014. Symetis generated revenues of CHF38.4m in 2016 and has succeeded in carving itself a place as the No. 3 TAVR player in Germany with a 13% market share – behind Edwards Lifesciences and Medtronic – and No. 4 in Europe, with a 7% market share – behind Edwards, Medtronic and Boston Scientific.

Symetis announced barely a week ago that it intended go ahead with an initial public offering on the Euronext Paris exchange to raise around $60m; the funds would have been used to further expand its manufacturing capabilities and provide it more resources to grow the business beyond Europe. *(Also see "Symetis Seeks $60m IPO To Make A Splash In Structural Heart" - Medtech Insight, 21 Mar, 2017.)*. While Boston Scientific's Lotus Valve system is also not yet available in the US, the company has been commercializing the device since 2013 in countries beyond Europe, including China. Symetis should gain significantly from having access to Boston Sci's ready-built international sales infrastructure.

Boston Scientific's senior management team took pains to drive home the message that the acquisition was all about portfolio-building and "doubling down" in a market worth more than $4bn, and not about hedging its bets against Lotus and the recent challenges with that platform. Boston Scientific issued a worldwide recall of all its Lotus Valve devices, from both commercial and clinical sites, after receiving reports that the pin that connects the valve to the delivery system may release prematurely. The company believes the premature pin-release is caused by excess tension in the pin mechanism due to a fault in the manufacturing process. *(Also see "Boston Scientific Pulls All Lotus TAVR Systems Off Shelves" - Medtech Insight, 23 Feb, 2017.)*. Prior to this recall, Boston Scientific had also pulled its newer-generation Lotus Edge device out of the market in November 2016 – two months after it was CE marked – due to a locking-down problem. *(Also see "Boston Scientific Stops Roll-Out Of Lotus Edge TAVR To Resolve Locking Problem" - Medtech Insight, 2 Nov, 2016.)*.

In a conference call to discuss the acquisition of Symetis, Boston Scientific Chairman and CEO Mike Mahoney insisted that the company was still on track with its plans to resolve the technical issues with Lotus and the clinical data that will be presented at the upcoming EuroPCR meeting in May are "very supportive" of the fixes and enhancements made to the systems, he said.

Lotus, Mahoney said, is still set to be reintroduced back to the market in Q4, as planned. The Symetis acquisition was all about "IP opportunities, not IP challenges" and it gives Boston Scientific more opportunities to strengthen its position in the TAVR market and achieve its overriding goal of becoming "a category leader." Mahoney affirmed categorically that the company would still have gone ahead with the deal, even if the Lotus recall had not happened. He commented that "this is not a new strategy for Boston Scientific," and that the company had always looked out for "clinical uniqueness and offerings by geography," he said. "By doing a deal like this, [it] reflects our strength in interventional cardiology."

M&A CASUALTY

One casualty of this transaction is Middle Peak Medical, a preclinical-stage transcatheter mitral valve repair company that Symetis had acquired just over a month ago. *(Also see "Europe's TAVR No. 4 Buys Into Mitral Valve Space" - Medtech Insight, 14 Feb, 2017.)*. When asked what Boston Scientific's plans were for Middle Peak, Kevin Ballinger, president of the group's interventional cardiology business, revealed that the Middle Peak was not included as part of the deal and it will be spun out of Symetis prior to the closing of the transaction.

Ballinger said that Boston Scientific already has its own investments in the mitral valve space, and while transcatheter mitral valve repair was a very interesting market, it involved a complicated etiology and did not offer a linear path to commercialization. Ballinger did not provide any more details about the fate of Middle Peak.

The Symetis acquisition is projected to close during the second quarter of 2017, subject to customary closing conditions. On an adjusted basis, the transaction is not expected to make an impact on Boston Scientific's bottom line until 2018, where it will be slightly accretive and then increasingly accretive thereafter.

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'All-Comers' Trial Finds Increased Risk Of Thrombosis With Abbott's Absorb BVS Stent

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Patients treated with **Abbott Laboratories Inc.**'s *Absorb GT1 BVS* bioabsorbable everolimus-eluting stent were 3.87 times as likely to develop a stent thrombosis as patients treated with Abbott's *Xience* everolimus-eluting metal stent within two years of implant in the Amsterdam Investigator-initiated Absorb Strategy All-comers (AIDA) trial.

The two-year results were published March 29 in the *New England Journal of Medicine*, just about a week after the two-year results of the ABSORB III trial showed Absorb was statistically inferior to Xience for the primary composite endpoint, as well as target-vessel myocardial infarction. The ABSORB III results, announced at the American College of Cardiology conference in Washington, DC, prompted the US FDA to send physicians a "Dear Doctor" letter highlighting the importance of proper patient selection and implant technique. *(Also see "ACC 2017: Disappointing Absorb Results Blamed On Implant Approach" - Medtech Insight, 26 Mar, 2017.)*

AIDA is a randomized, 1,845-patient investigator-initiated trial. It is led by Joanna Wykrzykowska of the Academic Medical Center in Amsterdam and supported by an unrestricted educational grant from Abbott. Wykrzykowska and colleagues randomized an "all-comers" population – intended to be representative of routine clinical practice – to treatment with either Absorb or Xience. The results published in NEJM were reported earlier than originally planned – after enrollment of all the patients, but before all the patient follow-up has been completed. "Because of the finding of an increased incidence of very late scaffold thrombosis, the data and safety monitoring board recommended early reporting of the study findings," Wykrzykowska et al. explain.

Absorb was non-inferior to Xience for the primary endpoint of two-year target-vessel failure, a composite of cardiac death, target-vessel myocardial infarction, or revascularization of the target-vessel. After a median follow-up of 707 days, 105 patients in the Absorb group and in 94 patients in the Xience group suffered a target-vessel failure. The two-year cumulative event rates were 11.7% in the Absorb group and 10.7% in the Xience group (p=0.43). Within two-years of the stent implant, 18 Absorb patients and in 23 Xience patients died of cardiac causes, 48 Absorb patients and 30 Xience patients suffered a target-vessel myocardial infarction, and target-vessel revascularization was necessary in 76 Absorb patients and 65 Xience patients.

> "There is little rationale to use bioresorbable vascular scaffolds at this time," says Debabrata Mukherjee of Texas Tech University.

However, 31 Absorb patients suffered a definite or probable device thrombosis compared with only 8 patients in the Xience group for two-year cumulative event rates of 3.5% vs. 0.9%, respectively, and a hazard ratio of 3.87 (p <0.001). Six of the Absorb patients with a thrombosis died of cardiac causes and 25 suffered a non-fatal myocardial infarction. Of the eight Xience patients suffering a thrombosis, two died of cardiac causes and six had nonfatal myocardial infarctions. Wykrzykowska et al. found no statistical relationship between device thrombosis and presenting symptoms, age, cardiovascular risk factors, lesion characteristics, or the time of randomization. Among the Absorb patients in AIDA who had definite or probable device thrombosis, 19% had a residual diameter stenosis of 30% or greater and among the patients who did not have device thrombosis, only 9% had a residual percent diameter stenosis of 30% or greater, a statistically significant difference.

In ABSORB III, 19% of the patients were treated for lesions with a reference vessel diameter of less than 2.25 mm, the minimum diameter recommended in Absorb's FDA-approved labeling. Post-hoc analysis of the results found that these smaller vessels are associated with an increased risk of target-vessel failure. The ABSORB III results also found that late-stent thrombosis was more likely in patients not treated with the recommended pre-dilation and post-dilation of the target vessel.

Absorb implantation took more time and required more contrast media, on average, than Xience implantation in the trial. "These findings attest to delivery challenges associated with scaffold implantation," Wykrzykowska et al. point out. Their analysis of the two-year AIDA results found no statistical relationship between the risk of stent thrombosis and vessel size of 2.25 mm or smaller, adequate device sizing, or post-dilation. "In our trial, scaffold thrombosis occurred regardless of implantation technique," the authors explain.

Nevertheless, in a prepared statement sent to *Medtech Insight* Abbott argues that "Enrollment in AIDA was completed in an era where the optimal deployment techniques were not well understood." The company points out that post-dilatation was performed in 26 of the 31 cases of stent thrombosis, but that the post-dilatation pressures used were below the current recommendation of at least 16

atmospheres. "More recent studies with contemporary deployment technique with post-dilatation pressures at 18 to 20 ATM are showing much lower rates of stent thrombosis."

In ABSORB III, OCT several patients with reference vessels narrower than 2.25 mm were treated with Absorb, even though the FDA approved labeling recommends against using it in these narrow vessels, because visual analysis overestimated the vessel's diameter. In AIDA, the inclusion criteria excluded patients with a reference vessel diameter under 2.5 mm or over 4.0 mm, but the reference vessel diameters were only estimated visually, without optical coherence tomography (OCT), Abbott points out.

"Analyses of Absorb trials from around the world have demonstrated that when implanted according to current instructions for use, outcomes were comparable to the best-in-class metallic drug-eluting stent, with a less than 1% rate of stent thrombosis," Abbott explains. "We look forward to results early next year of a more contemporary study (ABSORB IV) that is most reflective of current implantation techniques."

The AIDA investigators point out that a recent meta-analysis of 16,830 patients treated with Absorb showed a stent-thrombosis rate of 1.8% after a median follow-up of one year and that four cases (1.6% of patients) of definite stent thrombosis appeared in the ABSORB Japan trial between the one-year and two-year follow-up point. Also, the ABSORB II trial showed ongoing scaffold thrombosis events at up to three-years post-implant. *(Also see "TCT 2016: Three-Year ABSORB II Data Fail To Show The Hoped-For Long-Term Benefit Of Bioresorbable Stent" - Medtech Insight, 31 Oct, 2016.)*

"The causes of the higher rate of device thrombosis with [Absorb] than with [metal] stents are only partly understood. Incomplete lesion coverage, under-deployment, and malapposition have been observed with the use of optical coherence tomography in acute and subacute cases of scaffold thrombosis," Wykrzykowska et al. explain. "Thick stent struts, such as the 150-µm struts in the Absorb [stent], are associated with blood-flow alterations and thrombogenicity, especially when they are left malapposed. Late events might be related to a combination of non-embedded and non-absorbed [stent] struts in complex lesions and late structural discontinuity or device dismantling."

The authors note that extended dual antiplatelet therapy could reduce the risk of stent thrombosis in patients treated with Absorb. One-year results of the Dual Antiplatelet Therapy (DAPT) study, published in 2014, showed that prolongation of dual antiplatelet therapy reduced the risk of stent thrombosis in patients treated with first-generation metal drug-eluting stents compared to aspirin alone. Also, ABSORB II found no cases of very late scaffold thrombosis among the 63 Absorb patients who did not interrupt dual antiplatelet therapy for up to three years. "Further research is necessary to establish whether long-term dual antiplatelet therapy would prevent very late scaffold thrombosis," Wykrzykowska et al. conclude.

WILL BIOABSORBABLE-STENT OPPORTUNITY FADE AWAY?

The AIDA authors predict that newer generations of bioresorbable stents with thinner struts, different materials, and/or increased radial strength could overcome the limitations of Absorb. Companies working on next-generation bioabsorbable stents include **Elixir Medical Corp.** (*DESolve*), **REVA Medical Inc.** (*Fantom*) **Biotronik SE & Co. KG** (*Magmaris*). *(Also see "Robert Byrne: Absorb, Synergy, And The Future Of Coronary Stents" - Medtech Insight, 21 Sep, 2016.)* But "given the lack of putative benefit in the ABSORB Japan and ABSORB II trials, the advantage of bioresorbable technology over metallic stents remains to be established," Wykrzykowska et al. conclude.

In an accompanying editorial in NEJM, Debabrata Mukherjee of Texas Tech University,El Paso, argues that Absorb should only be implanted in patients who are able to stay on dual antiplatelet therapy for an extended period – perhaps up to three years – without an unacceptable risk of side effects. Practically, this limitation would mean that few, if any, patients should be treated with Absorb.

"The extended duration of dual antiplatelet therapy will come at the cost of a higher risk of bleeding, which will further attenuate any potential longer-term benefits of currently available bioresorbable scaffolds," Mukherjee explains. "Because the current generation of metallic drug-eluting stents is associated with excellent outcomes, there is little rationale to use bioresorbable vascular scaffolds at this time. To overcome the safety issues associated with the currently available devices, device manufacturers need to focus their efforts on developing newer generations of bioresorbable scaffolds that use thinner or narrower struts and that are composed of a different material that would allow for higher radial strength and faster rates of resorption."

Published online 03/30/17

NICE Endorses Boston Scientific's EnduraLife CRT-D Batteries

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The UK's National Institute for Health and Care Excellence (NICE) recommends treating heart failure patients needing a cardiac resynchronization therapy defibrillator with a CRT-D device powered by **Boston Scientific Corp.**'s *EnduraLife* battery technology.

EnduraLife is included in Boston Scientific's *Resonate* CRT-D devices with *SmartCRT* technology, including *Resonate X4*, *Charisma X4*, *Vigilant X4*, and *Momentum X4* CRT-D devices. The company launched the Resonate line Europe in February after receiving a CE mark.

EnduraLife can offer up to 14.7 years, or 13.3 years if the *MultiSite* pacing function is used, according to Boston Scientific. The company says that nine studies have shown that EnduraLife's lithium manganese dioxide technology offers the longest battery life of any CRT-D battery. It has 1.9 ampere-hours of battery capacity – compared to 1.4 Ah in **Abbott Laboratories Inc./St. Jude Medical Inc.** CRT-D devices and 1.0 Ah in **Medtronic PLC** CRT-D devices – and provides stable voltage over time.

NICE's new medical technologies guidance states that the published evidence supports the UK's National Health Service's adoption of EnduraLife-powered CRT-D devices, because "extended battery life is of clinical and patient benefit and associated with fewer replacement procedures." These devices should be an option for patients implanted with a CRT-D following NICE's 2014 guidance on CRT devices.

NICE's cost-modeling for EnduraLife-powered devices, based on published data, shows the lifespan of a CRT-D device is an important determinant of the overall treatment costs. "Assuming an average selling price of £12,404 across different devices, using EnduraLife-powered CRT-Ds may save between £2,120 and £5,627 per patient over 15 years, through a reduction in the need for replacement procedures," NICE concludes. "This could save the NHS in England around £6 million in the first 5 years."

Source: Boston Scientific Corp.

Boston Scientific's Resonate X4 CRT-D

Boston Scientific Chief Medical Officer Ken Stein told *Medtech Insight* that NICE's endorsement of the EnduraLife technology "leaves no room for doubt about the value of this feature."

The NICE guidance "transcends the company," he added. "It's important for medical technology as a whole because we do need to make sure people realize that advancements in technology can, at the same time, improve outcomes and reduce cost for the system," Stein said.

Stein believes NICE's opinion carries weight beyond the UK. "Outside of the UK, we really view this as just validating what we've been saying about these devices for years," he said. "It is our belief that one of the reasons that we've been having the success we've had in the past few years is that people are recognizing the improved longevity of our device and the value that brings to our patients. So we look on this as something that will accelerate that."

CRT-D is one of the technologies that helped Boston Scientific's cardiac rhythm management (CRM) division grow 3% year-over-year for all of 2016 and 8% in the fourth-quarter of 2016, year-over-year. During the company's third-quarter earnings call in October, CEO Michael Mahoney mentioned EnduraLife, as well as the company's CRM remote monitoring service, as two of the technological advantages allowing the company's CRM division to stay competitive with Medtronic and St. Jude.

"We promoted with proof, the unique benefits of our EnduraLife battery technology as being best in class and that's really been proven out from nine independent studies," the CEO said Oct. 26. "We've been very clear to the marketplace that we have very unique battery technology and also excellent remote monitoring. Those two features stand the test of time and really have been the anchor of our strategy for a number of years now."

During its Feb. 2, fourth-quarter 2016 earnings call, Boston Scientific projected the Resonate devices will be approved by US FDA in the third quarter of 2017.

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Infusion-Pump Maker Ivenix Closes Initial Tranche Of $50m Financing

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Ivenix Inc. has closed on the first tranche of $50m in equity financing, which will put the company on track to pursue FDA approval for its *Ivenix Infusion System*.

The money should also help the company expand its team to begin commercialization, pending FDA approval of a technology that CEO Stuart Randle earlier described to *Medtech Insight* as a complete redesign of legacy infusion pumps. He said the system will enhance dose accuracy and reduce the possibility of medication errors while also boosting clinician workflow.

The financing was led by two undisclosed investors, and also included participation from existing investors, **F-Prime Capital Partners** and **WuXi Healthcare Ventures**, among others. Ivenix announced on March 21 that remaining tranche funding will be crucial to meeting regulatory milestones and satisfying certain unnamed conditions.

Randle believes the Ivenix Infusion System is unique in that in offers a more comprehensive approach to address safety issues, which is a big problem in the estimated $6bn global infusion-pump market.

"A number of factors are fueling investors' interest in Ivenix, including the lack of innovation in the market, and the incidence of errors in infusion administration," Randle said in a company statement from March 21.

The Ivenix system is unique in that it offers a pneumatic pumping mechanism that can measure the flow of fluid and automatically adjusts to ensure accuracy. It also features a mechanism that, unlike other pumps on the market, delivers fluid independent of gravity, which means nurses don't have to be concerned about the height of the medication bag in relation to the pump.

Randle told *Medtech Insight* earlier that he considers Ivenix to be more of a health care IT company vs. an infusion-pump manufacturer, highlighting the system's integrated intelligence features that allow it to interact with larger health information systems or function as a standalone device.

Ketan Patel, a partner with F-Prime, said the demand for an innovative infusion system in health care is evident.

"We are proud to support Ivenix as the trailblazer working to bring a truly revolutionary solution to this underserved market," Patel said.

The infusion-pump market is dominated by three giants, **Baxter International Inc.**, **Becton Dickinson & Co.** and **Hospira Inc./ICU Medical Inc.**, all of which have developed infusion-pump systems that seek to address safety issues through interoperability.

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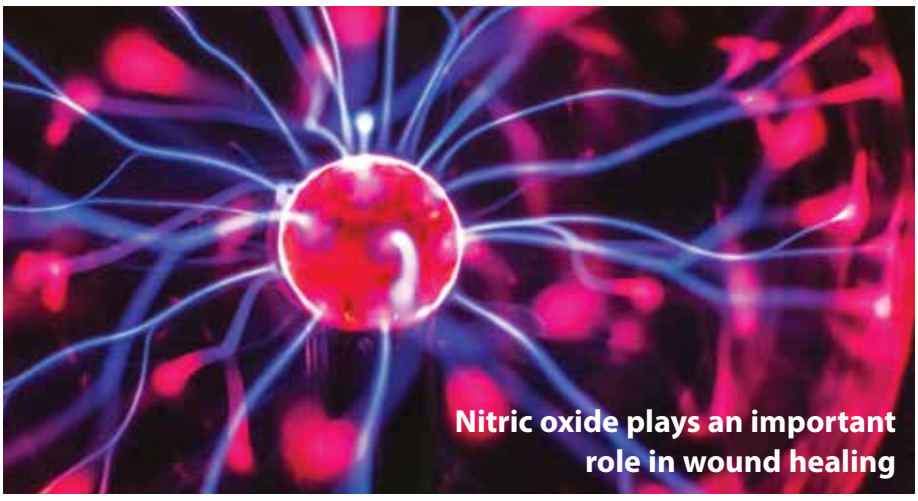
START-UP SPOTLIGHT:

Origin Inc., Healing Diabetic Foot Ulcers With Nitric Oxide Plasma Tech

CATHERINE LONGWORTH catherine.longworth@informa.com

Diabetic foot ulcers (DFUs) continue to be one of the major health challenges associated with diabetes patients and a major cost burden to healthcare providers. According to a 2014 study published in *Diabetes Care*, care of DFUs adds an additional $9-12bn to healthcare costs for diabetics. The condition, which is often the result of sensory neuropathy, is the leading cause of non-traumatic lower extremity amputations in the US, with approximately 7-15% of diabetics developing foot ulcers each year and up to 15% requiring amputation.



Nitric oxide plays an important role in wound healing

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One company hoping to address the challenge is US start-up, **Origin, Inc** which is pioneering a proprietary plasma solution for patients suffering from chronic DFUs. The New Jersey-based company is developing a device that produces and delivers therapeutic quantities of plasma-generated nitric oxide.

Nitric oxide (NO), a small radical formed from the amino acid L-arginine by three distinct isoforms of nitric oxide synthase, has been evidenced to play a key role in wound repair due to its functional influence on angiogenesis, inflammation, cell proliferation, matrix deposition and remodelling. The start-up aims to bring to market a handheld, computer-guided device that generates plasma NO from ambient room air within a defined plasma stream and delivers the NO directly to the target treatment area.

"The way the technology works is that at the point of delivering the therapy you use a high voltage electrical arc that is passed across a catalyst and a stream of ambient air," Betsy Hanna, Origin's chief operating officer tells *Medtech Insight*. "Air inside the room is pumped over the arc which then energizes the air stream and takes it to a highly energized plasma state. Because of the particular catalyst that is used, a plasma state is generated from the nitrogen and oxygen in the ambient air, generating a high therapeutic concentration of nitric oxide."

The company is kick-starting a US dose-ranging trial, GENESIS, to demonstrate the device's healing properties and optimize dose treatment for DFUs. The single-blinded, 27-week study will recruit up to 100 patients across 15 clinical sites in the US After a two-week run-in period, patients will then be randomized into one of four different dosing regimens or a standard of care treatment arm to assess efficacy and safety. Effectiveness will be measured by wound closure rate (in cm^2 of epithelium coverage per week) and wound closure percentage (effectiveness measures for the study analysed through a maximum of 12 weeks of treatment). Safety will be measured by wound-related adverse events, which include adverse events of all causes that affect the wound.

ORIGIN INC.
2 Research Way, Third Floor
Princeton, NJ 08540

Phone: 609 250 6000

Website: www.originww.com

Contact: Michael Preston, Chairman and CEO

Industry Segment: Wound care

Business: Nitric oxide plasma technology

Founded: 2010

Founders: Michael Preston, Howard Nelson, Alex Dolgopolsky, Trey Anthony, Michael Pohl

Employees: 17

Financing To-Date: $30m

Investors: Woodford Investment Management, private investors

Board of Directors: Michael Preston, David Dantzker, Howard Nelson, Vic Micati and Tony Brampton.

Scientific Advisory Board: Ferid Murad, Terry Treadwell, David Pompliano, Joel Friedman, Peter Vowden, Jerry Hutchinson, Anatoly B. Shekhter and Victor N. Vasilets.

"The objectives of this study are two-fold," explains Hanna. "Firstly, we are continuing to establish for the US FDA that there are no safety side effects to this therapy. The second thing we are doing with this study is we are looking to optimize the frequency and time of treatment for healing chronic DFUs. The study is designed with four different treatment arms to test multiple days a week and different treatment times to see if there is a healing rate response difference in any of those different frequency and time applications."

Origin Inc., founded under the name of Advanced Plasma Therapies, was established in 2010 to explore the broader area of plasma medicine. It was particularly interested in plasma's ability to deliver specific therapeutic molecules topically and the firm discovered a Russian plasma NO company that was using its technology for wound healing applications in Russia and Eastern Europe. The research behind the technology had won a Nobel prize and the technology's use in wound care was awarded the Russian Federation Prize for Science. In 2011, Origin's five founders secured an option to acquire the US patent for the technology and in 2014 began fundraising to expand development.

To date, Origin has raised in excess of $30m from private investors and from Woodford Investment Management, a leading healthcare fund based in Oxford, UK. At present, the company is raising additional funds to drive completion of this dose optimization study. If results prove to be positive, Origin aims to go through the US premarket approval process with the FDA.

As well as DFUs, Origin believes the technology could be used for multiple indications in wound care management, either as a replacement or in conjunction with other advanced therapies used for patients not responding to the current standard-of-care wound therapies.

Hanna says: "There is a huge unmet need in terms of healing of chronic ulcers but certainly with diabetic foot ulcers. We see this technology as something that can be used for wounds that are not healing after basic standard of care. Nitric oxide stimulates the body's natural healing mechanisms in place so we see this as something that can help accelerate and jump start healing where wounds otherwise are not repairing. The intent is to get that healing process going so you don't see a patient going down the path that ultimately leads in many cases to amputation."

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MDxHealth Prostate Cancer Test Identifies Increased Risk of Cancer Recurrence

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MDxHealth SA's *Confirm MDx* prostate cancer test identified men at increased risk of prostate cancer recurrence in a prospective study, suggesting the tissue-based test could help urologists monitor therapy response to improve the personalized treatment of castration resistant prostate cancer (CRPC).

Jack Schalken, director of urological research at the Radboud University in the Netherlands presented results from the study at the 2017 European Association of Urology Annual Congress in London, England.

The commercially available Confirm assay uses MDxHealth's proprietary technology platform Methylation-Specific-PCR (MSP) to assess methylation markers for prostate cancer, GSTP1, APC and RASSF1. The test distinguishes histologically benign biopsy cores from patients diagnosed with no cancer, low-volume cancer – a Gleason score of 6 – or higher-volume cancer – a Gleason score of 7.

The study showed that 47 men with CRPC had higher concentrations of plasma cell-free DNA (cfDNA) – fragments floating outside of cells in the bloodstream – and higher levels of methylation of biomarkers detected by the ConfirmMDx for Prostate Cancer test, than a control group of 30 healthy people. "The identification of reliable biomarkers for CRPC will ultimately help urologists to more effectively stratify patients in this population to receive the treatment that will provide the greatest potential for extending life," Schalken said.

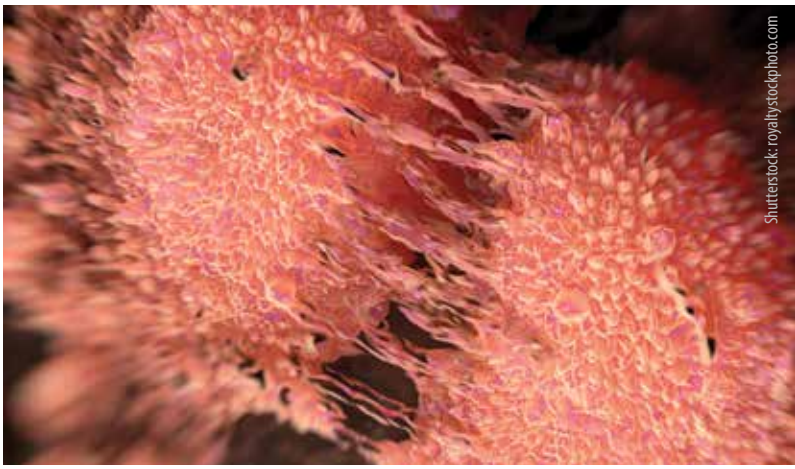
In the study, the median levels of cfDNA of men with CRPC were significantly higher than in the age-matched controls and men below 35 years of age. Hypermethylation of GSTP1 was observed in 91% of men with CRPC at baseline and were significantly higher than in the control patients. Methylated APC was also higher in men with CRPC at baseline versus the control group.

Patients were stratified into four groups to assess overall survival according to cfDNA concentration at baseline and GSTP1/APC response to treatment with chemotherapy, abiraterone, or enzalutamide. The group with both samples below the median had significantly less prostate cancer-related deaths.

The test is included in the NCCN (National Comprehensive Cancer Network) guidelines. "After the product made it to the NCCN guidelines, we saw a significant increase in the number of paid contracts but also an increase in the number of positive hospital policy decisions," MDx Health CEO Jan Groen told *Medtech Insight*.

Confirm is intended to aid urologists in identifying negative prostate biopsy results to reduce unnecessary repeat biopsy procedures. MDxHealth also markets *Select MDx*, an mRNA urine-based liquid biopsy test that provides the likelihood of detecting prostate cancer upon biopsy, and the probability of high-grade versus low-grade disease.

MDxHealth launched Select MDx in US and Europe in April 2016 and sells it through distributors in Asia, Latin America, and



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Israel. To accelerate adoption of the test, MDx Health signed a distribution agreement to make the test available to Lab21 clinical laboratory's urology clients in the UK. Under the terms of the agreement, Lab21 will serve as a non-exclusive distributor for SelectMDx in the UK. The liquid biopsy samples will be tested in MDxHealth's clinical diagnostic laboratory in the Netherlands and Lab21 will reimburse MDxHealth for all testing services.

"There's a huge unmet diagnostic need in prostate cancer. At present, the main way to diagnose prostate cancer is through the PSA screening test which measures the amount of prostate-specific antigen (PSA) in your blood," said Groen. "There's not a good tool available today to monitor the recurrence of prostate cancer because although the PSA test is a very sensitive test it's not highly specific. PSA levels can be elevated for a number of reasons, such as an enlarged prostate or medication and infections so if you use the PSA test as the screening methodology for prostate cancer, then there's a high likelihood that you are enrolling men into the queue of the biopsy procedure that most likely do not have prostate cancer whatsoever."

In 2017, the company will be expanding its line with the launch of *Assure MDx*, a urine test for bladder cancer in the US. The Assure test combines epigenetic and mutation biomarkers to predict the presence of bladder cancer in patients with micro or macroscopic hematuria. MDx predict the bladder cancer market in the US is worth more than half a billion dollars.

"It's not going to happen overnight but move forward to five to ten years from now you will see a high influx of biomarker specific assays that can provide a physician with better information – how to treat a patient, but also the next step is what type of medicine will be beneficial for the patient," Groen said.

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iCAD Touts PMA-Approved Tool As Time-Saver For 3D Breast Assessment

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US FDA approved **iCAD Inc.**'s PMA for its *PowerLook Tomo Detection* solution for breast tumor detection March 24. The firm says the product is the first ever concurrent-read computer aided detection (CAD) solution for digital breast tomosynthesis (DBT).

Current CAD systems are generally designed to analyze images from 2D mammography systems, which typically produce a total for four images per exam, after a scan. That approach has caused some frustration for radiologists who have adopted 3D tomosynthesis, which can product hundreds of images, because of the significantly longer read time. PowerLook analyzes each tomosynthesis plan concurrent with the scan, which the company says saves lots of time.

Approval of the tomo detection product "is a significant milestone and we are positioned to rapidly advance our commercial plan," said Ken Ferry, CEO of iCAD. FDA was able to approve the product for market use based on an October 2015-January 2016 clinical study in which 20 radiologists significantly reduced reading time of 240 tomosynthesis exams by an average of 29% more quickly with PowerLook, iCAD said.

"The product helps radiologists address a key concern relative to digital breast tomosynthesis in that DBT exams take significantly longer to read versus 2D mammography (FFDM) exams," Rodney Hawkins, iCAD VP of marketing, told *Medtech Insight*.

The system applies a form of machine learning called "deep learning" that relies on sophisticated algorithms trained with actual patient images to recognize the visual characteristics of cancer, iCAD says.

Three 3D tomosynthesis systems are currently approved in the US: *Selenia Dimensions* (**Hologic Inc.**); *SenoClaire* (**GE Healthcare**); and *MAMMOMAT Inspiration* (**Siemens AG**).

REIMBURSEMENT NOT A PRIMARY CONCERN

Medicare covers 3D tomosynthesis. It set a higher reimbursement rate for the service compared to 2D mammography scans starting in 2015. *(Also see "CMS Sets Higher Reimbursement Rates For 3D Mammography" - Medtech Insight, 3 Nov, 2014.)*

Private insurers, meanwhile, have been slower to come around to the new technology. Multiple plans still consider it an investigational technology that is not covered.

The effort to expand private-payer coverage of the technology was not helped by a January 2016 assessment of DBT by the US Preventive Services Task Force as either a primary breast cancer screening tool or as a supplement to a screen for women with dense breast tissue. The task force found "insufficient evidence on benefits and harms" of DBT. A higher "A" or "B" rating is necessary to require private payers on Affordable Care Act insurance exchanges to cover a service without cost-sharing. Also USPSTF recommendations can influence Medicare coverage policies.

Nonetheless, Hologic CEO Stephen MacMillan said in a recent TV interview, more private insurers have recently added coverage policies for breast tomosynthesis.

Regardless, reimbursement is not a primary concern for the PowerLook technology, according to iCAD's Hawkins, because the product is intended to improve the workflow for radiologists. "iCAD does not believe reimbursement for tomosynthesis CAD will be a primary driver for adoption," Hawkins said.

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ADVAMED-CHAIR EXIT INTERVIEW:

Vince Forlenza On Medtech Policy Priorities

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Vince Forlenza, president and CEO of **Becton Dickinson & Co.**, just finished his two-year term as chairman of AdvaMed's board. This month, he handed over the reins to Nadim Yared, CEO of **CVRx Inc.***(Also see "Q&A With Nadim Yared: AdvaMed's Next Chair On Capital Formation And Global Challenges" - Medtech Insight, 4 Aug, 2016.)*

In an exit- interview podcast with *Medtech Insight*, Forlenza discussed the experience, his advice for Yared and AdvaMed's approach to working with the Trump administration, among other topics.

Vince Forlenza

Medtech Insight: This is Ferdous Al-Faruque with Medtech Insight with Vincent Forlenza, CEO of BD, who recently stepped down as chair of AdvaMed's board. Vince, thank you very much for joining us today.

Vince Forlenza: My pleasure.

When you first joined the board of AdvaMed seven years ago, what were some big challenges that you faced for the industry and that you faced personally?

Forlenza: So there were two significant challenges. One certainly was MDUFA [user fees], and the issue really was, under the previous agreements, the industry had not seen improvement in approval times. And there was I think a lot of different opinions around how one might work with the FDA to actually improve performance. And so that was very intense when I joined the board.

The second one was I was joining the board, also I became chair of AdvaMedDx, and so building out the diagnostic piece of AdvaMed was an important goal for me, so that was a personal challenge that I had.

And then the third one was that, of course, I'd become president of BD at that time, so I was in a new role. So we had all of that going on.

Now, moving forward five years when you took the helm of AdvaMed's board of directors, what were unique challenges you saw then, and what did you decide to do about them?

Forlenza: Sure. Let me just start on the personal side, here. Of course, at the time that I was named board chair we also announced the acquisition of CareFusion. So we had a lot going on at BD that we had to manage, and luckily we've been able to do that quite successfully.

At the same time, from an AdvaMed and industry standpoint, it was really the challenge of the innovation ecosystem, for the industry was struggling a bit, and it there were still issues around the approval process for products, but it was more than that. Capital formation within the industry and the decrease in venture capital that we have seen was a major issue.

And, third, I think that we saw regulatory processes changing quite rapidly outside of the US especially in emerging markets.

So those are the three challenges. Now, number one was that, as part of stressing the ecosystem, of course we had the medical device tax. So we had to focus on that tax, getting that tax repealed. We were successful in having it suspended for two years. Obviously that's not good enough. It does not give us certainty moving forward and the kind of solution that we want. We'll continue working on that. That was number one.

Number two, we worked with Congress on the 21st Century Cures Act, and there are a number of improvements in terms of the approval process that I think are going to be helpful to the industry, the breakthrough pathway and whatnot, the centralized IRBs. So we're making progress on those issues.

The other very interesting one was the whole area of digital. And, of course, digital technology and the Internet of Things is becoming very important for the industry. So it was important to expand AdvaMed's membership approach to encompass digital, and of course we started a digital group within AdvaMed, and we also reached out to the FDA and we worked with them on their guidelines.

And then to finish up the question, on the international side, we strengthened our international organization, worked

with other trade associations around the globe on regulatory issues. And in places like China and India we actually became better organized, creating governing bodies, and whatnot. So I think we got a lot done.

The last challenge that I would talk to you about was it was time for MDUFA again. The good news here is that we had seen progress from the last agreement that I mentioned early on in my remarks, and in a collaborative partnership with the FDA – I'd describe it that way, there was a lot of negotiation back and forth obviously, and differences of opinion – but I believe we've gotten to a good place, and, of course, that sits with Congress now for approval.

As you know, the president proposed his budget in which he asks for an increase in user fees beyond what was agreed in the MDUFA IV user-fee agreement. What are your thoughts on that? How do you think that'll play out?

Forlenza: So I think the deal that was negotiated between the industry and FDA is the right deal. It's the right balance in terms of an increase for the industry, the right resources for the FDA, and there's some new content in there in terms of real-world evidence that the FDA was looking for, and to be very helpful to innovation over the long term. So I think what we did was right.

Now, in terms of what the administration has said, we've heard from the Senate [Health, Education, Labor and Pensions Committee] that they are supportive in terms of moving what we put together forward. So I'm encouraged to hear that, and I think that would be the right path.

Now that you're retiring from your chairmanship, what issues do you think your new chairman, Nadim Yared, and a board should focus on? Will it be some of the same ones that you've already talked about, or are there new challenges you're seeing in front of you?

Forlenza: Well, I would say that you basically have the same challenge. It is the stress on the innovation system that we talked about. Number one priority, of course, is going to be to get the medical device tax to the finish line for full repeal.

But I also think that when one steps back and looks at the entire time to get all the way through to reimbursement, it's not just working with the FDA, it's also working with CMS and how you bring those processes together to get technology in both a safe [and] effective manner but in a faster manner that also works for the venture community.

So I know that Nadim Yared is very focused on that, he ran Accel, which is one of the subsidiary boards for AdvaMed, the small-company board, so that's near and dear to his heart. I'm sure he'll be focused on that. I'm sure he'll also be focused on the international components as well as the regulatory process keeps changing around the world.

How do you feel about what you've accomplished in your time on the board and particularly as the board chair?

Forlenza: Well, I feel good that the board accomplished a lot. That we were able to get an agreement with the FDA on MDUFA, and I think that agreement builds upon what we have done in the past, and so I feel good about that, the passage of the 21st Century Cures Act, the suspension of the medical device tax.

Other interesting areas are, we've started work and we're making progress on AdvaMed's value framework initiative to better define the value of medical technology for multiple stakeholders: For the payers, for the providers, and of course so that the companies have a consistent way of expressing it.

One of the things I am most happy about, though, has to be that we hired Scott Whitaker to lead AdvaMed into the future. I think he's off to a wonderful start and is going to do a great job in the future.

One of the things, yesterday I was at this luncheon with the CEO of Pfizer, Ian Read, and he seems to take the position that the pharma companies are somewhat suffering or the health-care system itself is somewhat suffering because of the fact that insurance companies are not pulling their own weight. That's his opinion. Do you have a similar opinion of the way that the insurance companies operate inside the US?

Forlenza: No, I don't have that opinion about insurance companies. Our concern is that, as the government moves forward, that we create a sustainable health-care system that works for all of the entities and stakeholders within that system. It's got to work for patients, providers, insurance companies, the pharmaceutical industry, and of course the medical device industry.

Exactly how that shakes out, as we both know, that's a difficult road. But that's where it has to end up if we're going to continue to foster the innovation that patients need going forward.

So it's been a pretty dramatic political period to say the least in the U.S. in the past few months. What, if anything, is different about AdvaMed's D.C. strategy since the new administration and Congress took control? Also, how does that translate to a group like AdvaMed? Do you have any recommendations for Nadim as he engages in this current environment?

Forlenza: So, you know, we've built a strong foundation of working with Congress, and we're going to have to continue to work with Congress. You were talking about – or questioning about MDUFA. We have to work with them to get that finalized.

But there's a new administration in town, and we have to get to know the new leadership at CMS and at the FDA and HHS. We have to explain what is happening to our industry, what's happening to innovation within the industry, and then create that vision around how we can really promote life-sustaining, life-changing innovation.

And so we have a new series of actors, we have to get to know them, and we have to explain our industry, because we can't take

LISTEN

Visit our website at http://bit.ly/2nG1gZG to listen to our full interview with Vince Forlenza.

for granted that they know the particular challenges that we have. So it's going to be a balance.

So we're talking here today on Friday, March 24th, a day when the House Republican repeal and replace effort might be heading for a vote but does not seem to be headed for sure passage as we speak. The votes are still being counted. I want to point that out. Are you confident that the repeal and replace effort, as a mechanism to ultimately replace the device tax, is going to work? Or are there other potential avenues this year that you're looking at trying to repeal that before the tax returns in January of 2018? [Editors' note: *The health-care bill was ultimately removed from consideration due to lack of support.***]**

Forlenza: You know, we are hopeful that the process unfolding in Congress will move ahead and that the device tax will permanently be repealed. But it's not clear that will happen, and so we're going to have to also think about other ways of accomplishing this. And I wouldn't point to one particular legislative vehicle. I'm sure there will be multiple opportunities, and we're going to have to make sure that we're looking at all of those opportunities; not just an independent bill.

Are there any specific opportunities that you think are maybe second in line that you think would be highly successful based on the efforts that you're putting in?

Forlenza: You know, that's really too early to say. There's so much focus on the current activity.

Okay. So there's been a lot of focus by key congressional committees on Obamacare repeal, as we've kind of talked about. Do you worry that it's distracting from work on the time sensitive user fee reauthorization? We're now into March, and the reauthorization needs to be approved by Congress by the summer to avoid layoff notices going out to FDA staffers. So there is some urgency there. Do you have confidence the user fee agreement can be addressed by then?

Forlenza: Well, I think we have confidence that the user fee agreement can be addressed by then. But we're certainly concerned for the people working at the FDA, and we want clarity and they want clarity, so we're going to make sure that we're continuing to work with Congress to see that this happens.

So what is next for you? You're stepping off the chairmanship. Do you still plan to be involved as actively with AdvaMed?

Forlenza: Well, I'm a pretty busy guy anyway, but I'm going to stay involved with AdvaMed. I have a real passion for medtech innovation, so I very much enjoy participating on the board. I will be a board member. I will run one of the board committees. So I'm going to be highly involved.

Do you have any parting words for our listeners, many of whom are members of AdvaMed or have worked with AdvaMed?

Forlenza: Well, in my final statement as chairman, I said to the board that AdvaMed is a team sport, and advocating for technology for patients is a team sport. And what that means is that we all have to be highly involved. We have to have a voice. And so I was encouraging everyone to make sure that they are involved and they're working with their organizations to be involved with all the workgroups that we have. Because I think we both have a major challenge and a major opportunity with all the change that's happening in AdvaMed. So I'm looking forward to working with them as they move forward.

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House Subcommittee Grills Shuren On Facility Inspection Shortfalls

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Lawmakers pressed FDA Device Center Director Jeff Shuren on FDA's plans to improve the facility inspection process of device firms during a recent hearing.

During a March 28 session on device user-fee reauthorization, House Energy and Commerce Health Subcommittee members generally expressed support for the provisions of a Medical Device User Fee Agreement (MDUFA IV) and said they expect a clean reauthorization before July's end. But lawmakers asked pointed questions to Shuren about inefficiencies in the inspection process.

The line of questioning aligns with legislation that has now been introduced to improve consistency and transparency in the inspections process. *(Also see "New Bill Aims To Bring Consistency, Transparency To US FDA Inspections" - Medtech Insight, 16 Feb, 2017.)* In particular, the AdvaMed-endorsed legislation, introduced in the Senate last month (S. 404) and on March 28 in the House (H.R. 1736), calls for adopting a uniform FDA inspection process to ensure parity between foreign and domestic audits, notifying manufacturers in advance of records that will be requested during an inspection, and specifying a window of time for investigators to conduct their onsite inspections, among other requirements. The user-fee reauthorization offers a potential legislative vehicle for the inspections reforms.

While FDA's Quality System Inspection Technique offers firms a structure for how investigators will inspect with the goal of increasing audit consistency, many investigators stray from the technique, industry experts have told *Medtech Insight*. Investigator deviations from the technique mean less predictable audits and, quite possibly, unfavorable inspection outcomes for companies. *(Also see "FDA Investigators Play Fast And Loose With Quality System Inspection Technique, Experts Say – But Is It Par For The Course?" - Medtech Insight, 12 Dec, 2016.)*

INSPECTION PRESSURE

Rep. Markwayne Mullin, R-Okla., said at the hearing that he had been fielding complaints from his constituents about the lack of transparency, flexibility, and inconsistencies in US inspection processes at medtech plants, and has heard that foreign plant inspections are more efficient.

Shuren acknowledged that foreign plant inspections could take much less time, primarily because inspectors – who are under the direction of FDA's Office of Regulatory Affairs, not the Center for Devices and Radiological Health (CDRH) – are sent overseas primarily to focus on just one or two facility visits, while domestic inspectors frequently are overburdened by competing inspections.

"On the domestic side, an inspector may be finishing up on another inspection. Or, they get called away for a 'for cause' inspection," the device director explained. "That said, on average, both foreign and domestic inspections, are generally finished in four days or less; sometimes, in just one day," he added.

However, with a "program alignment" effort in the works internally at FDA, the quality of FDA inspections should improve, Shuren assured the congressman.

Under program alignment, facility inspections performed by the Office of Regulatory Affairs (ORA) will be structured along commodity-specific product lines – a historic change for the office, which conducts all of the agency's field activities. One of the plan's goals is to make inspections more predictable and consistent for investigators and manufacturers.

FDA Device Center Director Jeffrey Shuren testified at the March 28 House Energy and Commerce Committee, Health Subpanel hearing.

Photo credit: Fardous Al-Faruque

Rep. Diana DeGette, D-Colo., spoke about Trump administration barriers to MDUFA IV, 21st Century Cures Act implementation March 29 at the Press Club

"I do know that ORA is working with them [investigators], as part of our program alignment effort, and they are redoing the SOPs, so that it should reduce times on the inspections," Shuren said. The FDA device chief added that the program alignment would shift ORA away from directing the same investigators who conduct pharmaceutical and food plant inspections to also do device plant inspections – which leads to inconsistencies in the ways inspections are carried out.

"We're trying to get them to establish more vertical commodity inspections … and [investigators] would have more training, which would drive more consistencies in the inspections," Shuren remarked.

The head of FDA's device-center Office of Compliance said this week that US FDA investigators will begin inspecting device manufacturing facilities using the new program alignment inspectional approach on May 15. *(Also see "US FDA's 'Program Alignment' Inspection Scheme Coming Mid-May; Details Still Murky" - Medtech Insight, 29 Mar, 2017.)* But while FDA is "standing up" the program now, Shuren suggested at the hearing that it would take "two to three" years for the program to be fully up and running.

TOO LONG A WAIT?

But Rep. Mullin said two to three years was too long.

"I'm sorry, I just can't wrap my head around it," Mullin said. "When you see these companies, and the issues that are going on with them, why is it, once the [FDA] programs are fully stood up, that it should take so long? Companies want the program up, and want it implemented," he commented, adding, "Once you issue these SOPs, it should just be a matter of people willing to do their jobs that you pay them to do. If they have expertise in their fields, they should be able to do this. But it sounds like you are struggling, and the system is struggling."

Rep. Larry Bucshon, R-Ind., also told

Shuren, "I'd like to see more regularity in the routine inspection process that FDA performs."

Bucshon joined with Reps. Susan Brooks, R-Ind., Scott Peters, D-Calif., and G.K. Butterfield, D-N.C., in introducing H.R. 1736. The Senate bill was sponsored by Sens. Johnny Isakson, R-Ga., and Michael Bennet, D-Colo.

EXECUTIVE ORDER FOCUS

Meanwhile, Democrats, led by Rep. Diana DeGette, D-Colo., expressed concerns at the user-fee hearing about Trump administration efforts to deregulate FDA via executive orders, including one demanding removal of two regulations for every new one produced by an agency *(Also see "Trump's Two-For-One Reg Order Needs Agency Interpretation, Medtech Reg Experts Say" - Medtech Insight, 30 Jan, 2017.)*, and a second order calling for a hiring freeze. *(Also see "A Burning FDA Hiring Freeze Question: What About User-Fee-Supported Staff?" - Medtech Insight, 24 Jan, 2017.)* DeGette said the orders could hinder thorough implementation of the 21st Century Cures Act provisions, including its breakthrough devices program. *(Also see "21st Century Cures: Device Provisions" - Medtech Insight, 14 Dec, 2016.)*

Further, DeGette told reporters March 29 of concerns that representatives are planning to attach amendments on unrelated health-care issues to the user fee reauthorization bill, including a controversial amendment to defund Planned Parenthood.

"As you know, we've had now, three hearings on the different user fee statutes, and they've been substantive hearings," DeGette commented during an appearance at the National Press Club in Washington, DC. "The larger conversation about 'do you see those as a vehicle to move other types of legislation,' that's still happening, and I don't think it's been resolved in any way."

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Former Siemens CMO Tapped To Run US Health IT Policy

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The Trump administration has apparently selected former Siemens Healthcare USA Chief Medical Officer Donald Rucker to run US health IT policy. Although the Department of Health and Human Services will not confirm the appointment, Rucker is listed as the National Coordinator for Health IT on the HHS public directory.

Rucker, who most recently served as an adjunct professor at The Ohio State University in biomedical informatics and as a consultant, brings to the post not only extensive experience in developing and implementing electronic health record technology, but also a deep understanding of how EHR systems interact with other medical technology including imaging and patient-monitoring equipment.

A medical doctor, Rucker served as CMO at Siemens from 2000 to 2013. During his time at the company, he was integral to the firm's development of integrated IT systems and medical equipment, including advanced imaging. *(Also see "MedTech's Impact On Hospital Design Requires Early Planning, Communication, Stakeholders Say" - Medtech Insight, 3 Sep, 2012.)*

Rucker joins the Office of the National Coordinator for Health IT (ONC) at a time when the agency is charged with addressing continued challenges with health-record system-to-system interoperability and to implement reforms on this front enacted late last year by the 21st Century Cures Act. Included in the interoperability challenge is ensuring data from medical devices, including images and other monitored data can be properly captured in EHRs. Also, ONC is taking steps to incorporate unique device identifiers into EHRs as a means of tracking device use and outcomes. *(Also see "Providers Want Feds To Better Standardize Unique Device IDs" - Medtech Insight, 16 Dec, 2014.)*

Donald Rucker

ONC also funds projects to develop new digital-health software and devices and sets standards for the "meaningful use" program that provides Medicare incentives to encourage broader application of health IT in hospitals.

During his tenure at Siemens, Rucker represented the company and the medtech industry before Congress, at CMS, and at ONC, among other forums. Before joining the company, he practiced as an emergency department physician and, according to his Ohio State bio, he "co-developed the world's first Microsoft Windows-based electronic medical record."

Two former Obama administration ONC chiefs Farzad Mostashari, who served in the national coordinator post from 2011 through 2013, and Karen DeSalvo, who ran ONC from 2014 to 2016, tweeted March 31 in support of the Rucker appointment.

"Do good work, call on the #healthIT community, we will support you," Mostashari wrote.

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CONTINUED FROM PAGE 1

decisions or interact with industry based on that particular guidance," Boyd said, explaining why benefit-risk wasn't a factor in the 2016 warning letter count.

That guidance, "Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions," was issued by the agency on Dec. 27, 2016. *(Also see "FDA Finalizes Post-Market Benefit-Risk Guidance" - Medtech Insight, 30 Dec, 2016.)*

Part of an ongoing effort to harmonize benefit-risk considerations throughout CDRH, the new guidance proposes a broad framework for considering benefit-risk factors in medical device availability, compliance and enforcement decisions. *(Also see "Compliance 360° Part 8: Patient Influence On US FDA's Enforcement Strategy" - Medtech Insight, 27 Mar, 2017.)*

"Our benefit-risk guidance is going to change the way we make decisions and think about things for a variety of compliance and post-market assignments," Boyd said. (See box, "Benefit-Risk & Warning Letters," p. 22.)

And when it comes to Case for Quality, that initiative "has, in the past year, informed the way we interact with industry, but that's been going on for the past several years. There have been upward and downward and level trends while Case for Quality has been ongoing," he noted. "But we just can't point to either one of those two initiatives, for example, as the reason for any upward or downward trend over the past few years."

FDA staffing levels weren't attributed to the number of letters issued. "I do know that our analyst team talked to both managers and staff alike within the device center, within ORA, and we could not identify a single factor or event to attribute the drop to," Boyd added.

Carl Fischer, senior advisor in CDRH's compliance office, advised industry not to read too much into whether the few letters sent to firms last year is good news for manufacturers.

Fischer cautioned: "I think we need to be careful. We're talking about relatively small numbers of letters compared to the total number of manufacturers globally. So, 57 letters – or 60 letters, or 100 letters, or 120 letters, whatever it may be in a particular year – as a percentage of the overall manufacturer base, is not very high. So, I think there is some year-to-year variability, and even a fairly dramatic change in a particular year may not be a strong indicator."

> "Complaints are most often cited for failure to capture all sources of information as complaints; specifically, not considering telephone calls, emails, return goods, and/or servicing activities as a source of complaints," former FDAer Ricki Chase says.

Boyd agreed. "There are 25,700-plus registered device firms, about 12,000 of which are foreign, and 13,700 which are domestic. So, the number of inspections that we conduct and the number of warning letters that we issue to that establishment inventory, whether we're talking about a warning letter number of 121 or 57, is very small."

For his part, Boyd said he would be "hesitant to predict what's going to happen from one year to the next. We don't want to imply that we would expect to see a continued downward trend or a continued number of warning letters at this level. I wouldn't want to project that that's what will happen going forward."

DOMESTIC AUDITS DOWN 2% WHILE FOREIGN INSPECTIONS RISE 16%

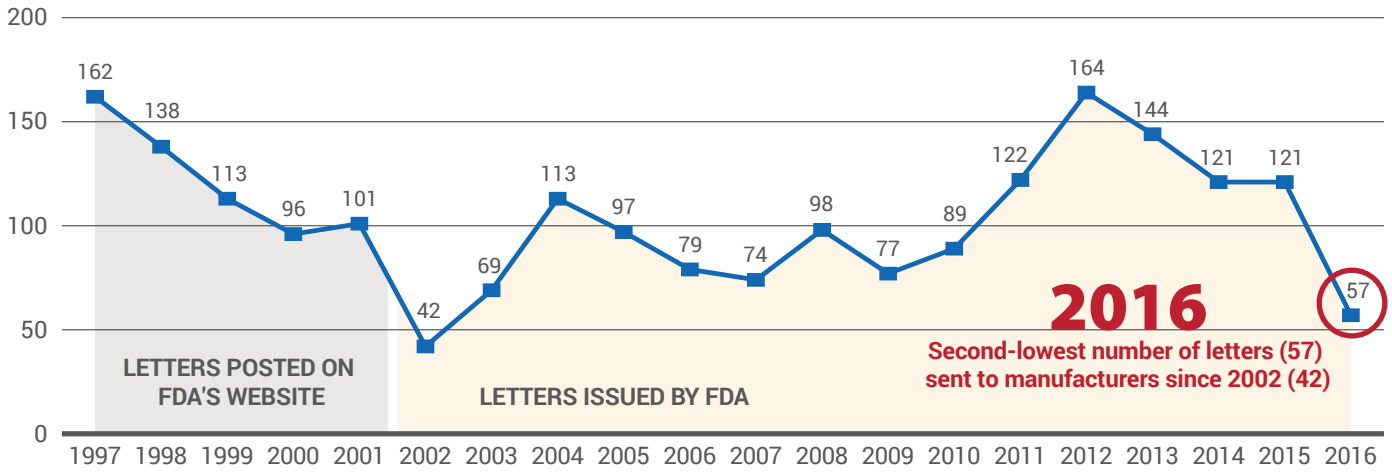
The 57 quality-related letters issued to firms last year was the product of 1,450 domestic (67%) and 725 (33%) foreign FDA inspections.

The 1,450 inspections conducted inside the US marks a 2% decrease from 2015, when there were 1,484 domestic audits. Yet inspections of foreign firms were up 16% last year, from the 620 foreign audits performed in 2015.

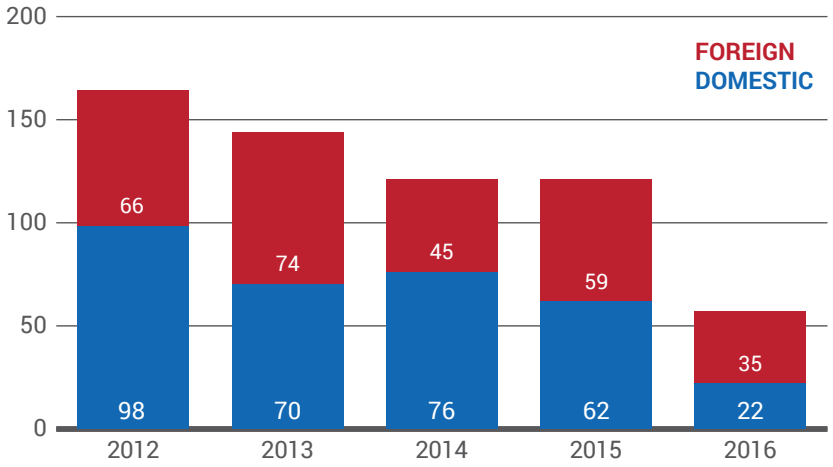
In March 2016, Boyd told *Medtech Insight* that FDA ultimately wants to achieve parity in the number of foreign and domestic inspections. *(Also see "Domestic, Foreign Manufacturers Achieve Virtual Quality-Related FDA Warning Letter Parity; Missive-Counting Methodologies Explained" - Medtech Insight, 28 Mar, 2016.)*

This year, Boyd said the agency is making progress on that goal. "For example, in 2016 we saw an increase in the proportion of foreign surveillance inspections that were conducted, from 620 in 2015 to 725 in 2016, with a decrease in domes-

Device Quality-Related Warning Letters, 1997-2016



Quality System Warning Letters: Domestic Vs. Foreign, 2012-2016



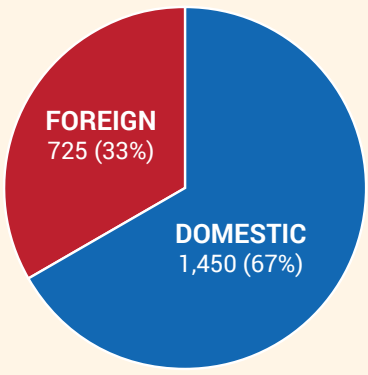
Top 3 Quality System Citations, 2016

1 CAPA

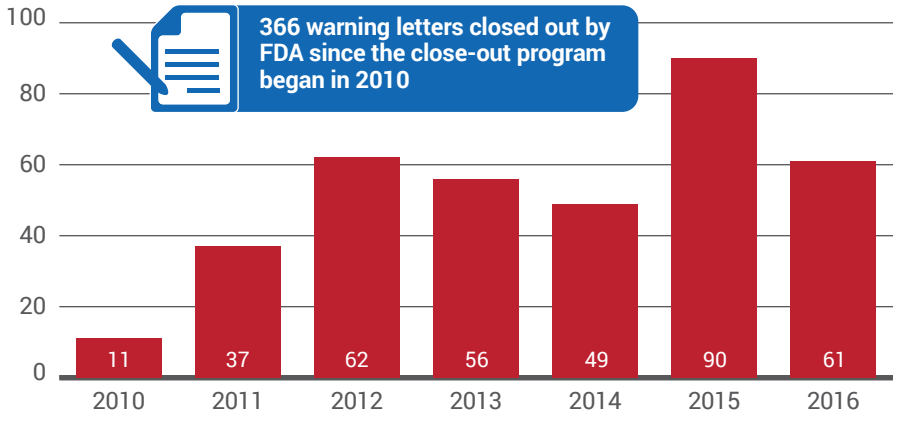
2 COMPLAINT HANDLING

3 NONCONFORMING PRODUCT

US FDA Inspections, 2016



Close-Out Letters, 2010-2016



Source: FDA and FDA websites

Benefit-Risk & Warning Letters

Although benefit-risk activities didn't affect warning letter counts in 2016, that doesn't mean benefit-risk won't play a role in issuing such missives moving forward.

"When it comes to our assessment of findings after a facility inspection, benefit-risk will inform the type of action we're going to take," FDA's Boyd said.

And that's not necessarily limited to a warning letter.

"There are a variety of advisory actions we can take when communicating issues to firms. It might include a regulatory meeting. It might include some other level of interaction based on the findings at a particular inspection," Boyd said. "So, I think the impact is going to be on how we assess the evidence that's before us in making a decision, whether to issue a warning letter or take some other action."

Further, "when evaluating the necessity for a warning letter, the guidance provides a framework we will use when internally documenting how we've gone about making that decision," Boyd said. "What are the factors related to benefit? What are the factors related to risk, and other considerations that led us to make the decision to issue a warning letter?"

tic surveillance inspections from 1,484 to 1,450. It wasn't a dramatic jump, but we're continuing to progress incrementally along that goal" of parity, he said.

Asked by *Medtech Insight* whether he truly believes there will one day be about the same number of US and non-US inspections, Boyd declined to be specific.

"I would anticipate continuing to see an incremental shift in the proportion of inspections that are conducted, but cannot predict when we expect to achieve parity between US and non-US inspections. There are a lot of things that are changing for both CDRH and our field operations right now that are going to play into how we go about making that shift."

Two such "things" that could shake up the number, frequency or location of inspections is the burgeoning Medical Device Single Audit Program (MDSAP) and FDA's in-the-works "program alignment" inspection initiative.

MDSAP, created by the International Medical Device Regulators Forum, allows firms to undergo one audit by an accredited third party to satisfy quality regulations for the US, Canada, Brazil, Japan and Australia.

Meanwhile, under program alignment – due to roll out on May 15 – facility inspections performed by ORA will be structured along commodity-specific product lines – a historic change for the office. One of the plan's goals is to make inspections more predictable and consistent for investigators and manufacturers. *(Also see "Compliance 360° Part 7: Factors Feeding Your Inspection Cycle – A New Paradigm" - Medtech Insight, 20 Mar, 2017.)*

TOP QUALITY SYSTEM VIOLATIONS IN 2016

Deviations from corrective and preventive action requirements – QSR Sec. 820.100 – were the No. 1 deficiency area cited in warning letters released last year, according to FDA.

"Inspection of the CAPA subsystem is required for each level of inspection following the Quality System Inspection Technique. Therefore, we would expect to see CAPA observations at the top of the list by the mere fact that they are subject of the most coverage," former FDA investigations branch director Ricki Chase says in the fifth installment of Compliance 360°, an eight-part podcast series from *Medtech Insight* on US FDA compliance and enforcement issues. *(Also see "Compliance 360° Part 5: Medical Device 483s – US FDA's Top 5 Observations" - Medtech Insight, 6 Mar, 2017.)*

For example, CAPA is always reviewed during an abbreviated Level 1 FDA inspection. Such an audit allows investigators to examine CAPA plus one other subsystem, including production and process controls, or design controls.

"With regards to CAPA, the most common specific observations include failure to complete a root-cause investigation, or the investigation is incomplete; failure to verify or validate the corrective action; and failure to review quality data," said Chase, now compliance practice director for Lachman Consultant Services, a firm she joined in June 2016 after spending 16 years at FDA, where she was also an investigator, medical device specialist and supervisory investigator.

In 2016, problems with complaint handling were the second most-frequent citation on warning letters, the agency said.

"Complaints are most often cited for failure to capture all sources of information as complaints; specifically, not considering telephone calls, emails, return goods, and/or servicing activities as a source of complaints," Chase says in the podcast. "Further, [firms] are cited for failure to process and handle complaints in a uniform manner."

When Chase inspected facilities as an FDA investigator, "I would frequently select complaints of a similar failure code or failure description to determine if uniform decision-making was being employed," she recalled. Further, "it has been observed that complaints for the same failure resulted in differing outcomes. A more serious concern is when one complaint failure results in a Medical Device Report, while a second complaint for the same failure does not."

Troubles with nonconforming product rounded out the agency's top three cites found on last year's warning letters.

Although FDA's Boyd shared those three most-violated quality system subsections with *Medtech Insight*, he declined to provide specific data. He said the agency plans to release online soon more information about the top citations found in 2016 warning letters.

CLOSE-OUT LETTERS ALSO DIP IN 2016

FDA handed out 61 warning-letter close-out letters last year, per a *Medtech Insight* tally of close-outs posted on the agency's website between Jan. 1, 2016, and Dec. 31, 2016.

That brings the total number of close-outs to 366 since FDA launched the close-out program in 2010. (See infographic, "Close-Out Letters, 2010-2016," p. 21.)

Under the program, the agency sends a letter to a company and posts it to its website when concerns outlined in a warning letter have been addressed. Such correspondence becomes part of a manufacturer's inspectional history.

The 61 close-out letters sent to firms in 2016 marks a 32% slide from 2015, when 90 close-outs were issued.

Boyd said the agency has not conducted an in-depth analysis of close-out letter trends. But when such an analysis is performed, "I would expect that we … wouldn't see a single event that we could attribute that decline to, other than maybe a correlation to a dip in the number of warning letters issued, which would necessarily reduce the number of close-outs that would need to be issued," he said.

For warning letters linked to quality, the agency typically re-inspects a manufacturer as a prerequisite to issuing a close-out letter. The FDA center or district office that sent the original warning letter is responsible for issuing the close-out letter.

"The other thing to keep in mind is, close-out letters are issued after a firm has addressed all problems at a particular facility, and the time it will take for a particular firm to address whatever is in a warning letter is going to depend on the number of items that are identified and the complexity of the issues that are discussed in the warning letter," Boyd said.

PACE OF LETTERS POSTED PICKS UP STEAM

Those in industry who track warning letters uploaded on FDA's website every Tuesday morning may have noticed a slowdown over the past few years in the number of missives cleared and posted online by the agency. *(Also see "Where Are The Warning Letters?" - Medtech Insight, 12 Aug, 2015.)*

> "There are different parts of our organization that are responsible for preparing and issuing warning letters, compared to who redacts and posts those letters. That handshake takes time," FDA's Sean Boyd says.

Last year, Boyd recognized that fewer letters were being posted and said there were internal touchpoints that FDA was looking at that might contribute to a lag in posting letters.

"We talked last year that there was a big backlog that [*Medtech Insight*] helped us realize, frankly. And we have made improvements to close that gap and reduce the backlog that we discussed then," Boyd said.

And it appears things are improving. In 2016, *Medtech Insight* counted 46 quality-related letters posted. That's about 80% of the 57 letters issued by the agency during that year. In 2015, there were 74 letters posted, which was just over 60% of the 121 sent out that year.

As of March 28, only 11 quality-related warning letters have been posted on FDA's website in 2017, according to *Medtech Insight*'s US FDA Warning Letter Data Tracker. Of those 11, nine were sent to firms from CDRH, and only one came from a district office: Los Angeles.

"There's always going to be a lag between when a warning letter is issued to a particular firm and then when it's posted online. There are different parts of our organization that are responsible for preparing and issuing warning letters, compared to who redacts and posts those letters. That handshake takes time," Boyd said.

"It should not take as much time as we discussed last year and, again, we have made improvements to internal processes to streamline and close that gap, and we don't have as large a backlog," he added. "But there are warning letters, as there always will be, waiting to be processed."

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