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US FDA INSPECTIONS & FDARA:

Will New Law Light The Way For Investigators?

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US medical device manufacturers hoping for a speedy FDA facility inspection sometimes encounter agency investigators who traipse in and out of firms at their leisure – auditing for perhaps only a day or two before returning at a later date to resume an inspection that could drag on for weeks.

A new law aims to put a stop to such arbitrary audit scheduling, along with other tweaks made to smoothen FDA's inspection process – but industry experts are of two minds as to whether any substantial changes will come about as a result.

Signed by President Trump on Aug. 18, the FDA Reauthorization Act (FDARA) not only continues and enhances the device, prescription drug, generic drug and biosimilar user-fee programs for another five years (beginning on Oct. 1), but it also makes other, largely industry-supported reforms to the agency – adjustments to FDA's approach to inspections and audit-planning being chief among them. *(Also see "MDUFA IV (And More) Is Law: Trump Signs A Health-Care Bill" - Medtech Insight, 18 Aug, 2017.)*

"The reason why [inspection-scheduling] is a pain point for the domestic market is because there are investigators who literally do not get out of those firms. They're in there inspecting forever," former FDA investigations branch director Ricki Chase told *Medtech Insight*. "As of recent times, there have been some investigators at FDA who go in and basically set up camp at a firm."

Chase is compliance practice director for Lachman Consultant Services, a firm she joined in 2016 after spending 16 years at FDA, where she was also an investigator, medical device specialist and supervisory investigator. (Chase is also the expert speaker for *Medtech Insight*'s suite of educational Compliance 360° podcasts on FDA compliance and enforcement issues.)

"It's an FDA audit. Investigators are not supposed to be part of the firm's embedded quality team. Rather, they're supposed to follow audit techniques as outlined in the Compliance Program Guidance Manual. That's how they're supposed to do their job," she said.

"The CPGM is very clear about how to conduct the inspection. The CPGM's clear intent is that investigators start an inspection and work every day to complete the inspection, and that there aren't large delays in the inspection process," Chase said. "Yet, there are investigators who dig in, and they end up being at a firm for weeks or months, or God knows how long."

> "There have been some investigators at FDA who go in and basically set up camp at a firm," former FDA investigations branch director Ricki Chase says.

FDA's Compliance Program Guidance Manual directs investigators on how to perform an inspection for a wide variety of products, including devices, drugs, biologics and vet medicine. For devices, the manual states that quality system inspections should "generally" be conducted using the agency's Quality System Inspection Technique.

QSIT is designed to make sure that investigators look at the most important compliance issues and ask pertinent questions

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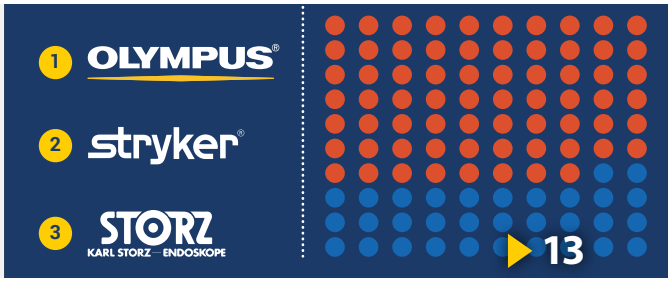

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Will New EU Standards Crisis Management Disrupt Industry's MDR Efforts?

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The European Commission wants to retain better control over the standards process by moving consultants who it pays to provide an essential service to the European standards organizations, CEN-CENELEC, from working within the standards bodies themselves to an independent body. This will impact the process for adopting medtech standards at a particularly complicated time for the device and diagnostics sector.

The consultants fulfill an administrative and quasi-legal role in the standards process in sectors that fall under the EU's so-called New Approach legislation, including the devices and diagnostics field. The purpose of this change is to make the consultants more directly accountable to the European Commission.

The Commission believes its action will result in a "more coherent … approach during assessment tasks … to avoid non-compliant harmonized standards the references of which the Commission cannot publish in the Official Journal."

The hope is that the Commission's decision will also put an end to confusion and uncertainty surrounding some medtech standards.

Some pivotal medtech standards, including the risk management standard, EN ISO 14971, started coming under criticism from the European Commission in 2011 and there has been an ongoing tension in the sector between the Commission and the standards organizations regarding the linkage between the standards and the Essential Requirements of the current device and diagnostic directives. This linkage, which is demonstrated in the so-called "Annex Z" of each standard – is the crucial element for using the standards to demonstrate conformity under the directives.

NEARLY NINE-MILLION EUROS

The European Commission has issued a notice for a tender, worth €8.75m (about $10.5m); the deadline to apply is October 16 . The duration of the contract is 48 months and subject to renewal.

There is speculation that one of the national standards organizations, such as DIN in Germany, might be interested in this kind of venture. It is not yet clear if the aim is to retain the existing CEN-CENELEC consultants under the new structure.

Ultimately, if these consultants are retained, they will be managed by the new organization rather than CEN-CENELEC, giving CEN-CENELEC a narrower standards-writing focus, rather than the full administrative burden of processing the standards as well.

A CRITICAL TIME

The new arrangement is likely to become active sometime between April and mid-May 2018, *Medtech Insight* sources suggest. It is essential that this transition is made as quickly and as smoothly as possible at this critical time for the medtech industry, which is preparing to meet the new Medical Device (MDR) and IVD Regulations (IVDR) that entered into force on May 25 of this year, and which will be fully enforced by May 2020 and 2022, respectively.

Standards are a cornerstone of the current and future EU medtech regulatory framework and some 300 harmonized standards have been developed to support the existing directives.

Standards are a cornerstone of the current and future EU medtech regulatory framework and some 300 harmonized standards have been developed to support the existing directives. Now, with the new regulations having entered into force, these existing "harmonized" standards will need to be reassessed against the new requirements, revised or dropped, and new standards may be needed as well.

Although it is likely to take at least a year, if not 18 months, from now for notified bodies to be designated under the new regulations, companies need to start preparing now to comply with the MDR and IVDR, including meeting the most up-to-date standards.

Any delay in standards-writing or in the adoption and harmonization process under the new regulations, or any uncertainties in the formal harmonization of some standards, could undermine industry's efforts and potentially legally expose companies if problems develop in the future.

WHY ARE THESE CONSULTANTS SO IMPORTANT?

The consultants in question are the first stop in the formal standards-harmonization system in the EU, so it is important they are working at full capacity as soon as possible. Harmonization is the process where standards are accepted by the Commission as giving a "presumption of conformity" with the relevant Essential Requirements.

As part of the harmonization process, the consultants review Annex Z of each standard after the standards have been written by the technical committees. Annex Z explains how the parts of the standard link with the directive's, or regulation's, Essential Requirements or parts of Essential Requirements, so that the standard can be used to claim a presumption of conformity with those requirements. (The Essential Requirements are renamed "General Safety and Performance Requirements" under the MDR.)

They look at the claims that the standards technical committee are making in the Annex Z and look at whether that is suitable for the standard to give the presumption of conformity to that piece

of the legislation and be harmonized. Where the consultant gives a positive assessment of a standard, this then goes to the Commission, which performs the final assessment. If the Commission agrees with the consultant, then the standard is published in the Official Journal of the European Union.

HEADING FOR A CRISIS?

Medtech Insight understands that there are about 300 standards that will, in theory, need reassessing. This would seem an unmanageable workload for this to happen within the transition time frame, so manufacturers who thought they had a standard giving them a presumption of conformity with the legislation may suddenly find they do not. Of course, these standards can still be used to demonstrate conformity, but will potentially lose the benefit of harmonization, at least for a while, for demonstrating conformity to the MDR

This may not be an issue for some product-specific standards, but it will be a problem for the sector, if horizontal standards such as the symbols standard, EN ISO 15223, or the risk management standard, EN ISO 14971, are not reassessed and harmonized as fast as possible against the new regulations.

LANDMARK MEDTECH STANDARDS MEETING

CEN-CENELEC have announced they are holding a meeting with stakeholders September 21 to examine the role of harmonized standards under the new Medical Device and IVD Regulations.

The aim, the standards organizations say, will be to identify ways in which different stakeholders may contribute to the successful transition to the regulations. Among other things, the meeting will address the compatibility of harmonized standards and common specifications under the new framework and be a forum to look at how standards will be managed during the transition, though this will probably come down to prioritization.

Participants at the meeting will also assess the lessons that can be learned from the harmonization process under the current medical device directives.

A panel discussion will focus on, among other things:

- What would be the alternative scenarios for harmonized standards and are these options viable for the stakeholders?
- What is role for international standards under the regulations?
- Will there be an impact of the recent rulings of the European Court of Justice on the use and impact of standards? *(Also see "EU Court Judgment Challenges Status of Standards: How Will It Hit Medtech?" - Medtech Insight, 12 Jun, 2017.)*

Published online 09/18/17

South Africa Reg System Finally Up And Running, But Medtechs Wary Over Costs

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Although South Africa's medical device and IVD establishments had several months to prepare for the impending licensing provision under the new national medtech regulatory system, it did not prevent the predictable last-minute rush. Some 500 applications for establishment licenses were filed in the two weeks prior to the August 24 deadline.

That doesn't mean the licenses have all been granted yet, given that the expert medical device committee at the National Department of Health (NDoH) meets only at pre-arranged times, but companies that applied in time will have received an acknowledgement (if not an actual license). This will stand as temporary license until licensing is granted, says NDoH. *(Also see "South African Medtech Reg: Pieces Coming Together, As August Deadline Approaches" - Medtech Insight, 21 Jun, 2017.)*

Licensing applies to all players in the medtech system – manufacturers, distributors, importers and exporters first, and wholesalers later – except for the smallest operations (i.e., those units that do not make, store or handle any product, such as sales branches). But the deadline has met (even though some companies might have missed it for lack of awareness): The licensing regulation is being enforced and used as a tool to regulate access to the market.

There are fears that the public sector might have been wrong-

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footed, as little appears to have been communicated to the provincial departments of health. For its part, SAMED, the South African medtech industry association, believes its members filed online in time; the group observes that private-sector operations seem to be better prepared than the public sector. For instance, Netcare Group, a private hospital, primary health care, emergency medical services and renal care group, was proactive in telling its suppliers that companies can no longer sell to it unless they have an ac-

knowledgement of their license application (or the license itself).

Another potential barrier to the market is the National Pharmaceutical Product Index (NAPPI) code, a universal national coding system that applies to private hospital groups for reimbursement purposes. As of August 24, a company can no longer get a new NAPPI code unless it is in possession of proof of application for its establishment license.

MEDTECH LAW UPDATE

Act 101, the Medicines and Related Substances Act 1965, as amended, was published on June 1. It incorporates Act 72 of 2008 and Act 14 of 2015. *(Also see "South Africa Medtech Reg: As New System Nears Finish Line, Device-Drug Distinctions Still Need Highlighting" - Medtech Insight, 20 Jun, 2017.)*

In essence, it brings into effect the long-awaited SAHPRA, the South African Health Products Regulatory Authority (SAHPRA), which will eventually replace the Medicines Control Council (MCC), headed by the registrar, Joey Gouws. SAHPRA has made a call for nominations to its board and for a CEO. MCC will exist until SAHPRA has had its first board meeting.

Industry group SAMED has welcomed the regulatory progress, but its executive officer Tanya Vogt notes that, despite guidelines to the contrary, the newly-amended act states that *all* South African device companies must be licensed. The guidelines had previously exempted class A (low-risk) product manufacturers from the need to hold an establishment license.

The new act takes precedence, says Vogt, which means that class A device manufacturers do need to obtain a license. However, the registrar told SAMED shortly after the deadline had passed that companies selling class A devices can submit a request for a "Section 36 exemption" from this requirement for a period of up to three months.

Several new guidelines have been amended or finalized, including documents on product risk classifications *(Also see "South Africa Medtech Regulations Published – Vital Next Steps Still Awaited" - Medtech Insight, 19 Jan, 2017.)*, adverse event reporting, and the quality manual. Proof of a quality manual needs to be submitted as part of the licensing application, but a quality management system (QMS) has not yet been finalized or published for South Africa. As a result, ISO 13485 is not yet being enforced and no date has a been established for this.

NEXT STAGES AND FEE CONCERNS

The next stages of regulation in South Africa will include licensing for wholesalers, which will be undertaken in 2018. Wholesalers can apply for a license as of 2018; as yet, only draft application forms and draft guidance are available.

A feature of the establishment licensing procedure is that manufacturers were asked to list their portfolios of products. Actual product *registration* is due to start in 2018, and the guidelines for this have now been published for comment. The product fee levels are not yet known. Vogt says, "We have liaised with government and conveyed that [our industry is not all big multinationals], in a bid to ensure that the product registration fees are reasonable." The fees will likely be issued before the end of 2017.

Establishment Licensing Costs

As stated in the Government Gazette of September 1, 2015 (Vol 603, No 39154) – section 6, applications for new five-year licenses are charged at:

- Manufacturing: Rand 21,800 ($1,683)
- Distribution: Rand 13,000 ($1,003)
- Wholesale: Rand 13,000
- Import: Rand 13,000 (for holders of certificates of registration)
- Export: Rand 13,000 (for holders of certificates of registration)

Applications for license renewals are charged at:

- Manufacturing: Rand 19,000 ($1,466)
- Distribution: Rand 10,900 ($841)
- Wholesale: Rand 10,900
- Import: Rand 8,000 ($617)
- Export: Rand 8,000

An annual retention fee is charged at Rand 3,000 ($232) – payable before the end of June each year – and there is a one-off license "collection" fee of Rand 2,900 ($224).

It is likely that manufacturers will have to absorb these extra costs, given the current economic climate and the pressure on all stakeholders to keep prices down. The private sector medical funders are also extremely powerful in influencing how much companies can charge in what is a very competitive market.

But while industry is being squeezed, there are no indications that manufacturers are planning to exit the market or close offices – not yet at least. But when ISO 13485 becomes a requirement, the costs will ramp up again. The plan is that CABs (conformity assessment bodies) will accredit companies to ISO 13485. SANAS, the national accreditation system, has already been training accreditors on the standard.

NEW START FOR SOUTH AFRICA

Nevertheless, South Africa has broached a new start for medtech regulation and, encouragingly, industry is getting an element of support from the authorities as this happens. NDoH held a major workshop for industry on July 13-14, a step SAMED had been pressing for, and it has reportedly been helpful in advising on the application process.

In addition, MCC has appointed Andrea Julsing Keyter as the new deputy director for medical devices, a posting which SAMED says has been a missing element in the national device oversight structure. Keyter and the MCC Registrar Gouws were among the high-level presenters at SAMED's 2017 annual conference, on August 23-24. Keyter will join SAHPRA, which will also be taking on further new staff and will be equipped with advanced IT infrastructures. The authority is due to set up separate departments, including one for medtech and IVDs, each with its own head.

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Medtech Can Help India 'Leapfrog Health-Care Constraints'

PENELOPE MACRAE

India has long struggled to provide even basic health care to its 1.3 billion citizens due to a lack of medical workers, shortage of facilities and treatment costs. But now, medical technology could come to the rescue and be a "disruptive" agent-of-change, helping India overcome infrastructure, manpower, geographic and affordability constraints, says a just-released report by global consultancy Deloitte.

The report, entitled *Medical Technology Shaping Healthcare For All in India*, cites development of easy-to-operate and technically advanced machines that can diagnose a patient in a village, transmit the data to a city physician who then can give advice via video conferencing. One new device, for instance, is a CT scan developed by **GE Healthcare** that uses 40% less power, produces less radiation, is 40% cheaper than imported equivalents and is 28% faster than conventional technologies. Another device made by **Sanray Technologies** is a digital X-ray imaging system that can be used by big hospitals and small clinics alike and costs a fraction of imported machines.

"The only way to break this (health care gap) cycle is to do something disruptive," said Charu Sehgal, a Deloitte partner and lead author of the report, which was made public by industry group CII at a New Delhi conference on Sept.7. "With a combination of mobile technology, IT and wearables, we have the means that give us potential to tackle these shortfalls in small towns and rural areas," Sehgal told *Medtech Insight* in an interview.

But in order to fully capitalize on this opportunity and scale it up to meet India's needs, concerted efforts by both government and industry would be needed.

CUTTING INDIA'S HEALTH BILL

Mindful of health care costs for its 1.3 billion population, the national government led by Narendra Modi recently declared one of its major health care priorities was prevention. That, according to Sehgal, is an area where medical technology can play a big role in screening and early diagnosis. "If you arrest the condition at the primary-care level, spending on secondary and tertiary care falls along with morbidity," she noted.

To spur the industry, Deloitte suggests the government could provide faster grant of patents, financial incentives for industry and innovation support by providing capital and infrastructure to med-tech start-ups. It could stimulate local medical-device demand through health insurance programs as well as collaborate with the private sector through public-private partnerships [PPP] models. For its part, industry needs to keep its focus on customizing its business models to suit Indian markets. India is an expert at "frugal engineering" — producing more affordable devices while meeting threshold quality standards.

Right now, nearly all top 40 global medical devices firm have an Indian presence, holding a share of 40-50% share of consumables, instruments and appliances and as much as 80-90% of other sub-segments. However, most MNCs have their production outside India and import products for the Indian market, something Modi's government is keen to change to bolster its Make-in-India initiative aimed at job-creation.

Products like needles, catheters, X-ray apparatus and dental instruments, which provide sizeable opportunities and require moderate technological expertise, should be prioritized for 'Make-in-India', Deloitte suggested. "Products with low-to-medium sophisticated technology could be quick wins… (and) impact the import bill significantly" as they account for 46% of med-tech imports in India valued at INR83bn ($1.3bn).

NEED SCALE TO ACHIEVE VIABILITY

"From a technology point of view, we're not lacking," Sehgal said. But "whether you're a domestic or international firm, you need a certain scale… if volumes aren't enough, if there's demand for only 50 units of a certain equipment piece, I'm not going to manufacture it because it won't be viable," she said.

"In the value chain, we should attack the low- and medium-end first because for high-end manufacturing (like CT scans and MRI machines), high-end spare parts, we don't have the required eco-system, we'll still have to import components. So do it stages."

In addition, the government needs to make the Indian investment landscape more inviting for both foreign and domestic device-makers in the capital-intensive segment. The government's already taken some steps, by allowing 100% foreign direct investment under the automatic approval route in the med-tech segment, correcting the inverted-duty structure for some devices and setting up med-tech parks in three states and testing labs in two. There's huge potential to be tapped with per-capita device spending just $3 compared to $178 in China, $340 in the US and $47 on an annual average globally.

Still, investment flows have been modest. In the nine months from December 2014 to August 2015 after the government allowed 100% FDI, investment was just $85m, a miniscule 0.5% of total FDI and 5.4% of health care FDI. Since then, import reliance has fallen only marginally to 70% in 2016 from 75% in 2014, Deloitte said. Part of the problem is that the country still ranks 130 out of 189 nations on the ease-of-doing business scale due to complex bureaucracy, ambiguous labor laws and high lead-time for clearances.

Also, crucially, experts blame low public health-care expenditure. The government allocates just 1% of GDP to public health care, one of the weakest rates globally and there's scant health insurance penetration, further dampening demand for health-care services and allied medical technology.

PUBLIC NEED NOT GETTING 'CONVERTED TO DEMAND'

"The need's very high. The need's not getting converted to demand, in large measure because of affordability. In a country like India where 300m people still live on less than $1.50 a day, there's no way you can expect people to pay for these servic-

es out-of-pocket. So some recognition of insurance and financing has to be there. Financing's a huge issue," Sehgal said.

Another constraint for investors right now is there's no independent regulatory authority for medical devices. In addition, imposition of price controls on certain medical devices has created uncertainty. Six months after slapping stiff price curbs on cardiac stents, the government last month slashed costs of knee implants by nearly 70%, saying the action was necessary to end "unethical profiteering."

"Health is a public good… this is out-of-pocket expenditure for so many, it (the government) tries to find ways to create more affordability," Sehgal said. But unexpected "actions create anxiety.... The industry doesn't know what's next… it (regulation) needs a more holistic solution," she added.

'THERE'LL BE NO RED-TAPISM'

At the medical conference where the Deloitte report was released, the health minister of Uttar Pradesh highlighted the potential for the med-tech industry in the country's most populous state of 200 million that's also one of the nation's poorest and has a per capita spend of $7 a person every year on health care, 70% lower than the Indian average.

The minister, Siddharth Nath Singh, is currently at the center of a major row over high child mortality at public hospitals in Uttar Pradesh. Indian media reported 23 children died last month in a single day at one state-run institution where oxygen supplies ran out because nobody apparently paid the supplier's bill. Singh told the audience there was nothing exceptional about the death toll, blaming it on endemic Japanese encephalitis, and insisted the deaths' timeline indicated no connection to the lack of oxygen.

Singh conceded though public healthcare infrastructure is "in a shambles" in the state, which is led by a controversial Hindu nationalist monk-turned-politician, and said he was determined to turn around the situation. "I'm absolutely keen" to have public-private partnerships (PPPs), he said, but added patient prices under such schemes would have to be "affordable."

Corporate profits could come from the enormous number of patients, said Singh, a grandson of a former Indian premier. "Volume is the real catalyst to push PPP," he said.

Inviting med-tech manufacturers to help improve the state's health-care system, the victim of neglect by successive governments, Singh promised: "There'll be no red-tapism. Only a red carpet awaits you." He said he planned to announce a med-tech tender in two months that could offer a potential market worth "perhaps INR10bn."

Singh added with Uttar Pradesh having 84% fewer specialists and 50% fewer nursing staff than required, he could use all the help possible from medical technology.

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Inivata Names New Chief Operations Officer

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Cancer genomics company **Inivata Ltd.** has named Jamie Platt as Chief Operations Officer. Platt will be based at Inivata's CLIA lab in Research Triangle Park, North Carolina and help drive operational activities across the organization in both the UK and the US to accelerate use the company's *InVision* liquid biopsy platform

Most recently, Platt served as CEO and founder of BRIDGenomics, providng contract commercialization services. She also served two years as VP-Genomics Solutions for Molecular Pathology Laboratory Network, and previously spent over 12 years with **Quest Diagnostics Inc.**, developing infectious disease diagnostics and shaping the companies advanced sequencing strategy and product portfolio. Platt has a PhD in molecular and cellular biology from Oregon State University.

Her appointment follows the news that Inivata will partner with Carolinas HealthCare System's Levine Cancer Institute to form the Inivata Knowledge Accumulation Network (IKAN), a global network of world-leading cancer centres working in partnership with Inivata to assess the potential of liquid biopsy to transform cancer care and improve patient outcomes.

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Axonics Appoints Chief Medical Officer

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Neuromodulation company **Axonics Modulation Technologies Inc.** has appointed urogynecologist and clinical researcher Karen Noblett as Chief Medical Officer.

The Irvine, CA-based company is developing the first rechargeable sacral neuromodulation system for the treatment of urinary and bowel dysfunction. Noblett has conducted extensive research within female pelvic medicine, with an emphasis on sacral neuromodulation for the treatment of patients with refractory overactive bladder, urinary retention, and bowel dysfunction.

In the previous 20 years, she served as a clinical professor, practicing physician, fellowship director and CMO at the University of California – Irvine. Most recently she was founding Chair of the Department of Obstetrics and Gynecology at the University of California – Riverside's School of Medicine.

She will continue to serve in academic leadership roles with the American Urogynecology Society and the American Board of OB/GYN.

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Philly Pelvic Mesh Trial Ends In Largest Verdict Against Ethicon

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The sixth and most-recent product liability suit concerning **Ethicon Endo-Surgery Inc.** pelvic mesh products ended in Philadelphia on Sept. 7 with a jury's $57m verdict against the company.

The case was brought by Pennsylvania resident Ella Ebaugh, who says she experiences ongoing pain and incontinence caused when two implants of Ethicon's *TVT* and *TVT-Secur* mesh eroded into her body. She required three surgeries to remove the mesh.

The $57m figure, which includes $50m in punitive and $7.1 in compensatory damages, is by far the largest of the five judgements entered against the **Johnson & Johnson** subsidiary since bellweather cases began in the Court of Common Pleas as part of multi-district litigation in late 2015. Ethicon won one case, while the others ended in jury awards to plaintiffs of $12.5m, $13.5m, $20m and $2.1m. *(Also see "Court Rules Against Ethicon In Pelvic Mesh Case, But Without Punitive Damages" - Medtech Insight, 2 Jun, 2017.)*

Trial evidence showed that J&J failed to inform doctors about complications and injuries connected to the mesh and "intentionally manipulated" literature to disguise problems with the products, Kila Baldwin of Kline & Specter told The Philadelphia Inquirer. Baldwin represented Ebaugh in the case.

Ethicon plans to appeal the case.

"We believe the evidence showed Ethicon's TVT and TVT-Secur devices were properly designed, Ethicon acted appropriately and responsibly in the research, development and marketing of the products, and the products were not the cause of the plaintiff's continuing medical problems," said company spokeswoman Kristen Wallace.

Ethicon is unusual among device manufacturers in continuing to fight mesh cases in court, industry monitors say. Other manufacturers, such as Endo International, have moved to settle most cases brought against them. *(Also see "Pelvic Mesh Cases Continue As Endo Moves To Settle" - Medtech Insight, 11 Aug, 2017.)*

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Pacts In Medtech, July/August 2017

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While the traditional summer recess led to an expected drop in the number of alliances in August, there was still a good level of activity from medtech players – with a couple of joint ventures thrown in – right through the month before.

Among the industry pacts sealed in July was between Japan's **Pentax Medical** and a much smaller and younger Chinese player, **Aohua Photoelectricity Endoscope,** to create a joint venture focused on flexible medical endoscopes. The new company, named Pentax-Aohua Medical Technologies Co., Ltd, will draw on its two owners' established expertise and sales presence in this area to develop and sell flexible medical endoscopes initially to the emerging markets in Asia, Latin America, Eastern Europe, Middle East and North Africa. The companies estimate the global flexible endoscopy market to be worth approximately $2.5bn and growing at an average rate of of 5% annually. "The emerging markets are a key growth driver [of demand for flexible endoscopes], based on increasing population, economic growth, investments in medical institutions and infrastructure and a growing demand for minimally invasive procedures," they said. Aohua and Pentax both offer endoscopes for use across different medical fields, but the JV will initially focus on the area of gastroenterology, where the devices will be used to detect cancer and other GI diseases.

Another JV deal struck in July was between Swiss nutritional conglomerate **Nestle SA** and French microbiome specialist **Enterome Bioscience SA** . *(Also see "Nestlé's Microbiome Interest Deepens With Enterome JV" - Medtech Insight, 12 Jul, 2017.)*. The buzz around microbiome – the mini-ecosystem of microbes that inhabit a particular environment within our anatomy – has grown increasingly louder of the last few years, with increasing evidence indicating a link between changes in the microbiome and their impact on an individual's health. The JV, called **Microbiome Diagnostics Partners**, will focus on accelerating the commercialization of Enterome's microbiome-based diagnostic platform, which include biomarkers associated with gastrointestinal disorders like Crohn's and inflammatory bowel disease and those associated with liver disease.

Other B2B alliances forged in the last two months were spread across a variety of sectors: China-based **Kindstar Global Co. Ltd.** and Israel's **ImmunArray Pvt. Ltd.,** entered an agreement in which Kindstar will help conduct clinical trials of ImmunArray's lupus diagnostic *SLE-Key Rule-Out* in China and once approved by regulators in that country, will be the product's exclusive distributor for that market; **Adin Dental Implant Systems Ltd.** licensed exclusive worldwide rights to **SpineGuard SA**'s *Dynamic Surgical Guidance* (*DSG*) technology for use in dental implantation indi-

cations; in women's health, **Viveve Medical Inc.** licensed exclusive US marketing and distribution rights to **InControl Medical LLC**'s FDA-approved devices for incontinence and improving the strength of pelvic floor muscles; and maker of the *da Vinci* surgical robot **Intuitive Surgical Inc** continued to expand its IP portfolio by gaining exclusive global rights to **JustRight Surgical LLC.'s** energy-based vessel sealing and tissue stapling technologies for use in minimally invasive surgical robotics.

Below are more details of these and other key medtech industry/R&D alliances in July and August:

PLAYERS	PACT	PRODUCT SECTOR
JULY		
Baxter International Inc., Ramot at Tel Aviv University Ltd. (a division of Tel Aviv University) & Tel Aviv Sourasky Medical Center	**Baxter International Inc.**, through **Ramot at Tel Aviv University Ltd.** (the tech transfer unit of **Tel Aviv University** (TAU)), will exclusively license surgical technologies from both TAU and the TAU-affiliated **Tel Aviv Sourasky Medical Center** (TASMC).	Surgery
Enterome Bioscience SA, Microbiome Diagnostics Partners, Nestle Health Science SA (a division of Nestle SA) & Prometheus Laboratories Inc. (a division of Nestle SA)	**Enterome Bioscience SA** and **Nestle Health Science SA** are creating a 50/50 joint venture named **Microbiome Diagnostics Partners** (MDP).	IVD
ImmunArray Pvt. Ltd. & Kindstar Global Co. Ltd.	China-based **Kindstar Global Co. Ltd.** and **ImmunArray Pvt. Ltd.** entered into a development and licensing deal surrounding ImmunArray's marketed lupus diagnostic *SLE-Key Rule-Out.*	IVD
Gene Editing Institute (a division of Christiana Care Health System) & NovellusDx	To support its work in the cancer diagnostics space, **NovellusDx** licensed a gene editing technology from the **Gene Editing Institute**, part of **Christiana Care Health System**'s **Helen F. Graham Cancer Center & Research Institute**.	IVD
Adin Dental Implant Systems Ltd. & SpineGuard SA	**Adin Dental Implant Systems Ltd.** licensed exclusive worldwide rights to **SpineGuard SA**'s *Dynamic Surgical Guidance (DSG)* technology for use in dental implantation indications.	Dental
Pentax-Aohua Medical Technologies Co. Ltd., Pentax Medical (a division of Hoya Corp.) & Shanghai Aohua Photoelectricity Endoscope Co. Ltd.	**Pentax Medical** and **Shanghai Aohua Photoelectricity Endoscope Co. Ltd.** (Aohua) established an Asian joint venture that will focus on flexible endoscopy.	Diagnostic imaging
Smith & Nephew & University of Hull	**Smith & Nephew PLC** and the University of Hull entered a long-term collaboration to create a wound care research cluster and to promote more R&D into advanced wound care technologies.	Wound care
AUGUST		
InControl Medical LLC & Viveve Medical Inc.	**Viveve Medical Inc.** licensed exclusive US marketing and distribution rights to **InControl Medical LLC**'s FDA-approved devices for incontinence and improving the strength of pelvic floor muscles.	Women's health
Intuitive Surgical Inc. & JustRight Surgical LLC	**JustRight Surgical LLC** granted **Intuitive Surgical Inc.** exclusive global rights to IP pertaining to its energy-based vessel sealing and tissue stapling technologies, which are used in the minimally invasive surgical robotics field.	Surgery

Source: Strategic Transactions

Medtronic Launches Advanced Chronic Pain Management System

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Medtronic PLC announced Sept. 18 that it is launching the next generation of its *Intellis* chronic pain management system in the US, following PMA supplement approval by FDA.

Medtronic is already the largest vendor of implantable SCS devices, with sales of about $535.3m and a 30.2% market share in 2016, data from *Meddevicetracker* shows. **Boston Scientific Corp.** and **Abbott Laboratories Inc./St. Jude Medical Inc.** are close behind in the competitive market, and upstart **Nevro Corp.** has gained significant share since 2015, when it introduced its next-generation *Senza SCS* system, a next-generation high-frequency waveform technology that has shown promise in treating back and leg. *(Also see "Pain Management II: Competition Intensifies For Spinal Cord Stim Market's Big Three" - Medtech Insight, 23 May, 2017.)*

The Intellis platform is Medtronic's next play to increase its lead. Among other advances touted by the firm, the platform uses the smallest fully implantable SCS neurostimulator. In addition, it integrates Medtronic's proprietary *SureScan MRI* technology, which allows MRI scans anywhere on the body under certain conditions. It also incorporates technology that allows therapy doses and locations to be automatically adjusted based on body position. It can be used with Medtronic's *EvolveSM* workflow, and is managed wirelessly via a secure **Samsung Electronics Co. Ltd.** tablet interface.

Photo credit: Medtronic PLC

MEDTONIC'S *INTELLIS* SPINAL CORD STIMULATION PLATFORM

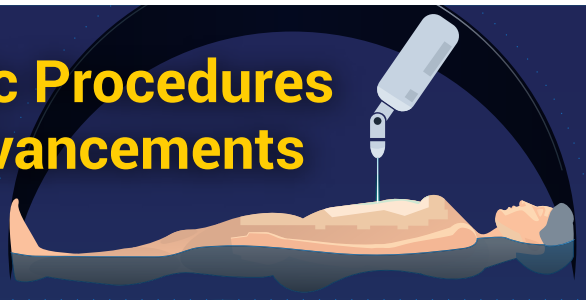
Samsung and Medtronic's neuromodulation division first announced an alliance to develop digital health solutions for chronic pain, movement disorders and incontinence in 2015. The companies are also collaborating on diabetes management apps. *(Also see "Diabetes Market Sees Advances In CGMs, Artificial Pancreas Systems, And Connectivity" - Medtech Insight, 24 Aug, 2015.)*

A common patient complaint about SCS has been battery life and recharge problems, which Intellis addresses by using a battery that can be fully recharged in one hour and lets physicians estimate recharge intervals based on therapy settings, Medtronic says.

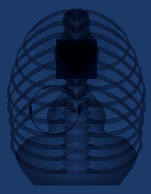
The company is pushing it as a possible alternative to addictive opioids. "This platform represents a welcome new option for managing some kinds of chronic pain. New non-opioid treatment options are important given the national crisis related to opioid abuse," said Lance Roy, a Duke University Medical Center pain medicine specialist, in a Medtronic release.

Published online 09/18/17

Endoscopic General & Pelvic Procedures Driven By Technological Advancements

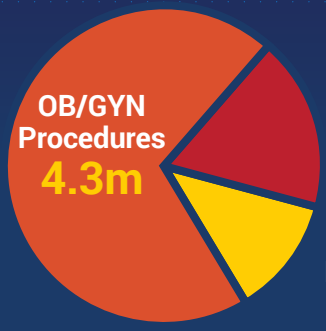


Sales of endoscopic and pelvic surgery devices will continue to grow at a modest rate. The conversion from open to endoscopic surgery continues to be fueled by technological advancements and patient demand for less invasive surgeries, driving sales of these devices to reach $15.8bn by 2021.



24.3m

No. of endoscopic general and pelvic procedures performed worldwide in 2016

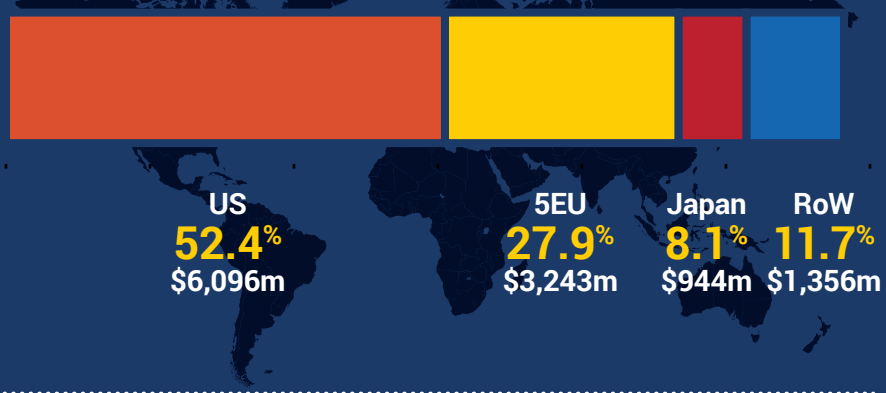


$11.6bn
2016

GLOBAL SALES FOR ENDOSCOPIC GENERAL AND PELVIC SURGERY

$15.8bn
2021

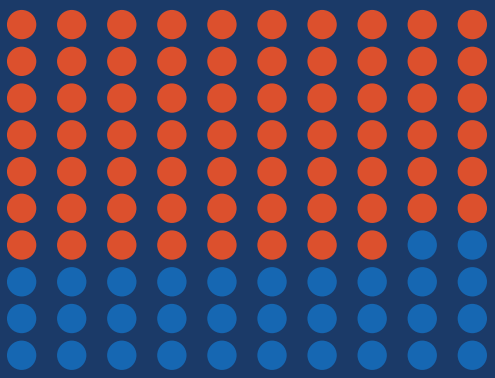
GEOGRAPHIC BREAKDOWN BY COUNTRY/REGION, 2016



THE ENDOSCOPES MARKET HAS TOP 3 PLAYERS

1. OLYMPUS®
2. stryker®
3. STORZ KARL STORZ — ENDOSKOPE

78% TOTAL MARKET SHARE HELD BY THE TOP 3 PLAYERS



753,000

Approximate number of surgical procedures performed worldwide using Intuitive Surgical's da Vinci robotic surgery system.

Source: Meddevicetracker's General and Pelvic Endoscopic Surgery Devices Market

OUS APPROVALS ANALYSIS:

Medtronic, MicroPort Lead August's Line-Up Of International Approvals

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Cardiovascular devices accounted for more than one-third of the medical device approvals announced outside the United States in August, including three from **Medtronic PLC** and four from **MicroPort Scientific Corp.**, according to *Medtech Insight*'s Approvals Tracker.

Medtronic announced both the CE mark and US FDA approval of its *Avalus* pericardial aortic surgical valve on Aug 2. The company plans to launch it commercially later this year.

Avalus is based on established Medtronic bioprosthetic valve technology and is also the only stented surgical aortic valve on the market approved to be compatible with MRI. It has a supra-annular design to limit central regurgitation, an interior-mounted leaflet and frame design to enhance durability, a low-profile valve design, streamlined valve holder, and a one-cut release to facilitate implantation

The approvals are based on results of the 1,100-patient, 40-site PERIGON non-randomized, prospective study. One-year results, presented by Joseph Sabik of the UH Cleveland Medical Center at the American Association of Thoracic Surgery annual meeting in May, showed low rates of adverse valve-related events with high survival and improved hemodynamic performance. However, an analysis by the PERIGON investigators of 686 patients in the trial (total of 459.5 valve-years), published in the *European Journal of Cardiothoracic Surgery* in September showed that the linearized rates of all and major hemorrhage were above acceptable rates, possibly related to long-term anticoagulation for non-valvular indications and the length of follow-up, according to the authors. At the same time, the analysis showed survival with Avalus at one year was 96.4% and that the patients showed good functional recovery, and hemodynamic performance was within expected range.

On Aug 21, Medtronic also announced the European launch of its *Attain Stability Quad MRI SureScan* left heart leads, with a separate CE mark for the ventricular tachycardia and fibrillation indication, and another for the bradycardia, ventricular dyssynchrony, and conduction defects indication.

The lead features a side-helix designed to be fixated precisely in veins of various sizes and four electrodes to allow the implanting physician to optimization the location of stimulation on the heart. It is approved as compatible with 3T MRI. The market launch has been limited so far, with the first commercial implants performed at Haukeland University Hospital, Bergen, Norway.

Medtronic also announced the launch of an international clinical study to evaluate the safety and effectiveness of these leads in heart-failure patients. The study will enroll up to 471 patients across 56 sites in the United States, Canada, Europe, Hong Kong and Malaysia to evaluate the number of patients that have appropriate pacing capture thresholds in at least two programming configurations.

Shanghai-based Microport Scientific announced four cardiovascular approvals during August.

On Aug 11, MicroPort announced it had obtained regulatory approval from the China Food and Drug Administration for its in-house developed *PathBuilder* transseptal guiding introducer and needle, used to access the femoral vein and cardiac chambers during radiofrequency ablation of cardiac arrhythmias. This approval the first "passive appliance" MicroPort's electrophysiology division has launched in China.

Three days later, MicroPort announced that Malaysia's Medical Device Authority approved its *Foxtrot Pro* balloon dilatation catheter and *Firehawk* rapamycin target eluting coronary stent system. This is the first time MicroPort has earned approvals in Malaysia since that country introduced local device regulations last year. *(Also see "Malaysia's New Medtech Regulatory System Imminent - And No More Extension This Time " - Medtech Insight, 21 Jun, 2016.)* Both Firehawk and Foxtrot Pro were previously available in Malaysia, before gaining MDA-approval, as the local authority allows products with CE mark to be sold to some hospitals.

Firehawk features an in-groove abluminal coating design and target-eluting technique to achieve the same clinical efficacy with significantly lower drug-loading than earlier drug-eluting stents. It is available in six diameters from 2.25mm to 4.00mm and six lengths from 13mm to 38mm. Foxtrot Pro is a rapid exchange balloon with seamless laser-welded connections a "stripe" hydrophilic coating to make it easier to cross and inflate in complex lesions. It is compatible with any 6F guiding catheter, and comes in six diameters from 1.5mm to 4.0mm and five lengths from 6mm to 25mm.

Also, MicroPort announced Aug 17 that its *Firefighter* coronary balloon dilation catheter has been approved by Argentina's National Administration of Drugs, Foods and Medical Devices for sale in that country. Firefighter also has a CE mark, as well as approval from Brazil's National Health Surveillance Agency, and approval from the China Food and Drug Administration.

Firefighter is a rapid-exchange catheter indicated for dilating stenotic atherosclerotic lesions in coronary arteries, and can be used in combination with Firehawk. It is available in 12 diameters, from 1.0mm to 4.0mm, and four lengths from 6mm to 20mm.

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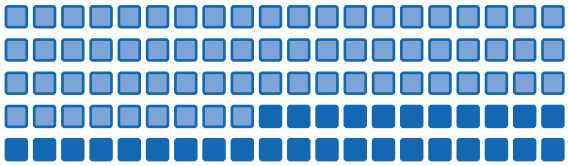
OUS Approvals

AUGUST 2017

According to Medtech Insight's Approvals Tracker, Cardiovascular devices were the most common type of device appearing in the list of non-US approvals in August 2017.

7 NON-US, NON-EUORPEAN APPROVALS
16 CE Marks

The 23 non-US approvals in August 2017 was below average for what has typically been a slow month in years past according to Medtech Insight's Approvals Tracker. There were only 17 in August 2016 and just 12 non-US approvals recorded in August 2015.



2017 is on pace for 351 non-US approvals, compared to 241 in 2016.

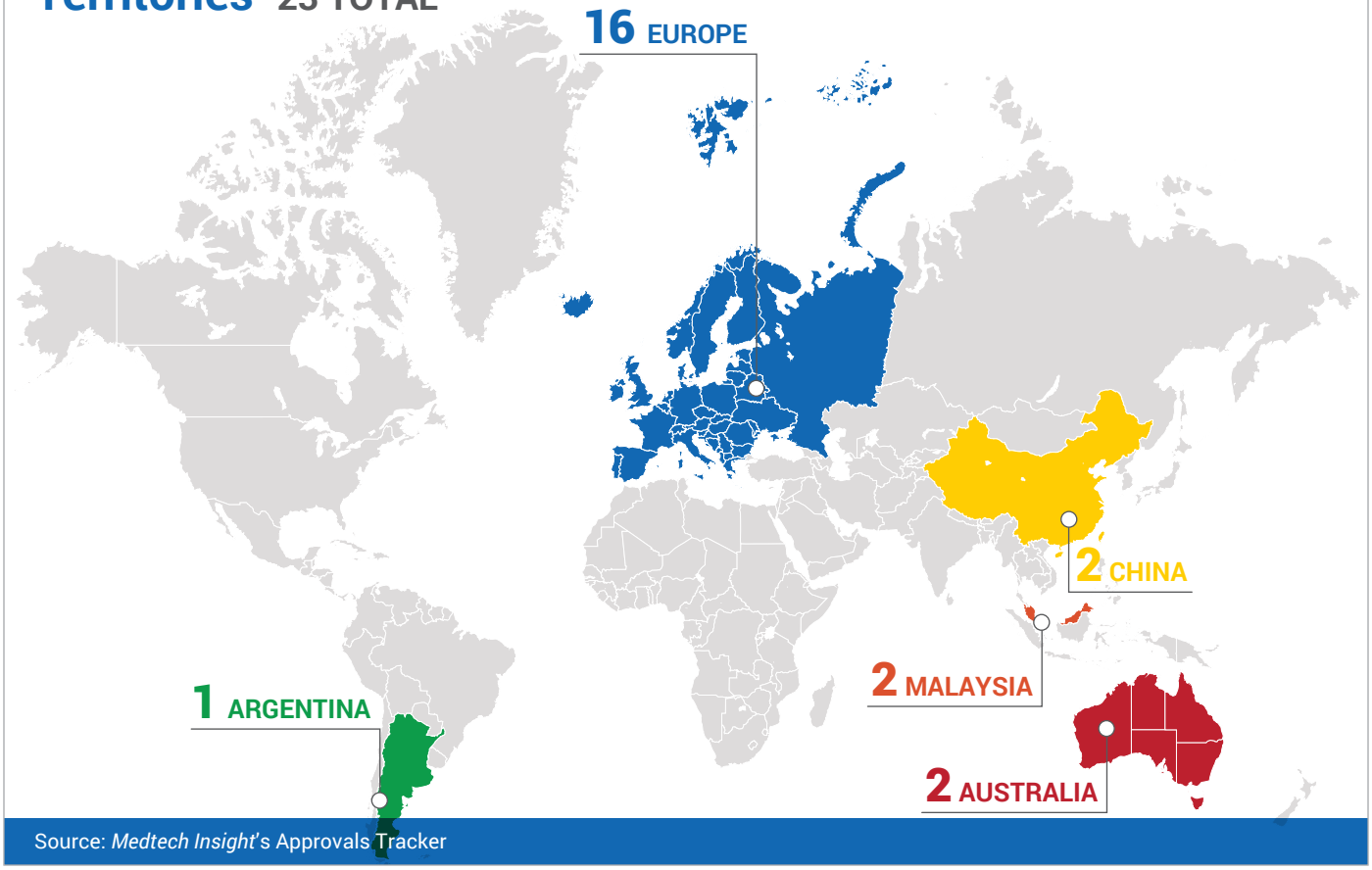
2017 2016

Product Categories

23 TOTAL

- **9** Cardiology
- **4** Anesthesia
- **3** Oncology
- **3** Orthopedics
- **1** Drug-Delivery
- **1** Neurology/Neurostim
- **1** Obesity
- **1** Surgery

Territories 23 TOTAL



Source: *Medtech Insight*'s Approvals Tracker

US APPROVALS ANALYSIS:

Abbott Leads Another Strong Month For Novel Approvals

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US FDA approved five original PMAs in August, continuing its rapid pace for the year.

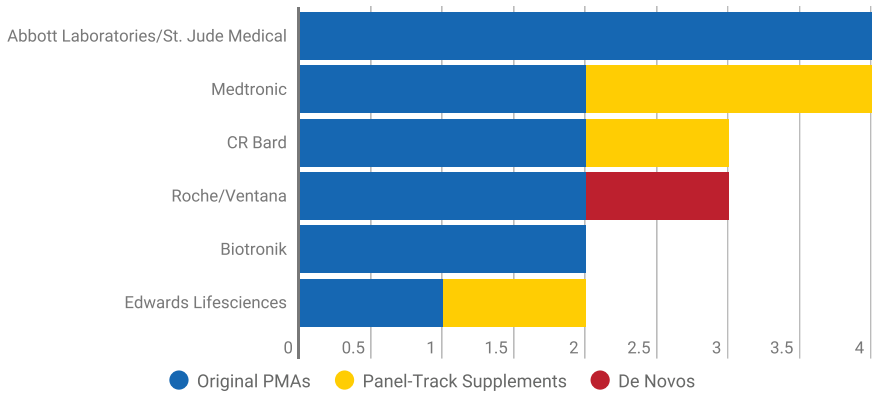
Abbott Laboratories Inc. achieved two of the data-heavy, high-risk device approvals, one for its highly anticipated *HeartMate 3* left-ventricular assist device, and the other for a companion diagnostic to an acute myeloid leukemia drug.

Heartmate 3 is a next-generation LVAD that is central to Abbott's growth plan for its legacy Thoratec business. The device, which is smaller than HeartMate II and associated with a comparatively lower rate of pump thrombosis, was approved Aug. 23 by FDA as a bridge to heart transplant or myocardial recovery, but not yet as a longer-term "destination" therapy.

FIGURE 1

2017 Novel-Device Approvals: Company Rankings

Firms with at least two novel-device approvals through August 2017.



*Source: **Medtech Insight**'s Approvals Tracker*

FIGURE 2

Novel Device Approvals, August 2017

PRODUCT	COMPANY	APPROVAL DATE	SUBMISSION TYPE	CLINICAL SPECIALTY	INDICATION
DUROLANE	Bioventus LLC	08/29/17	Original PMA	Orthopedic	Approval for the treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacological therapy or simple analgesics, such as acetominophen.
LUTONIX® 035 Drug Coated Balloon PTA Catheter, Model 9010	LUTONIX	08/25/17	Original PMA	Cardiovascular	Approval for the treatment of stenotic lesions in dysfunctional native arteriovenous dialysis fistulae that are 4 mm to 12 mm in diameter and up to 80 mm in length. Also indicated for percutaneous transluminal angioplasty.
t:slim X2 Insulin Pump with Dexcom G5 Mobile CGM	Tandem Diabetes Care, Inc.)	08/25/17	Panel-Track PMA Supplement	Clinical Chemistry	Approval for the use with the Dexcom G5 Mobile CGM, modifying the indications for use to include pediatric patients ages 6-11 years and replace adjunctive with non-adjunctive CGM use (i.e., replace fingerstick blood glucose testing for diabetes treatment decisions).
HeartMate 3™ Left Ventricular Assist System	Thoratec Corporation	08/23/17	Original PMA	Cardiovascular	Approval providing short-term hemodynamic support (e.g., bridge to transplant or bridge to myocardial recovery) in patients with advanced refractory left ventricular heart failure.
PrecisionTM and Spectra WaveWriterTM Spinal Cord Stimulation (SCS) Systems	Boston Scientific Corp.	08/11/17	Panel-Track PMA Supplement	Neurology	Approval for expanding indications to include Complex Regional Pain Syndrome (CRPS) Types I and II and the following associated conditions and etiologies: radicular pain syndrome, radiculopathies resulting in pain secondary to failed back syndrome or herniated disc, epidural fibrosis, degenerative disc disease (herniated disc pain refractory to conservative and surgical interventions), arachnoiditis, and multiple back surgeries.

PRODUCT	COMPANY	APPROVAL DATE	SUBMISSION TYPE	CLINICAL SPECIALTY	INDICATION
REVANESSE ULTRA	PROLLENIUM MEDICAL TECHNOLOGIES INC.	08/04/17	Original PMA	General & Plastic Surgery	Approval for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds, such as nasolabial folds, in adults 22 years of age or more.
Abbott RealTime IDH2	Abbott Molecular Inc.	08/01/17	Original PMA	Molecular Genetics	Approval as an aid in identifying acute myeloid leukemia patients with an isocitrate dehydrogenase-2 (IDH2) mutation for treatment with Idhifa (enasidenib). For use with the Abbott m2000rt System.
ID-FISH Plasmodium Genus Test Kit, ID-FISH Plasmodium Falciparum And P. Vivax Combo Test Kit	ID-FISH TECHNOLOGY, INC	08/18/17	Direct De Novo	Microbiology	"Approval to aid in the diagnosis of malaria and to aid in the differential diagnosis of P. falciparum and P. vivax infection for patients with a clinical history and signs and symptoms consistent with malaria."

*Source: **Medtech Insight**'s Approvals Tracker*

The current market-leading HeartMate II will continue to be the only pump FDA-approved for destination therapy on the market for the time being, but **Medtronic PLC** is hoping to compete on that indication soon. FDA's decision on Medtronic's *HVAD* destination therapy submission is expected by the end of the year. *(Also see "Medtronic Set To Compete With Abbott/St Jude In VADs After Buying HeartWare " - Medtech Insight, 27 Jun, 2016.)* HeartMate III gained a CE mark in Europe in 2015 for both bridge-to-transplant and destination therapies in 2015. *(Also see "Next-Gen HeartMate Launches In St. Jude's Portfolio" - Medtech Insight, 12 Oct, 2015.).*

The US approval of the next-generation device might help balance a recent step backward in Abbott's cardiovascular portfolio, with the firm's withdrawal of its *Absorb* bioabsorbable stent from global markets. *(Also see "Abbott Pulls Absorb Stent Off The Market, Citing Low Sales" - Medtech Insight, 8 Sep, 2017.)*

Abbott's companion diagnostic approval, meanwhile, came Aug. 1, for the firm's *RealTime IDH2* assay, labeled to select candidates for treatment with the concurrently approved *Idhifa* (enasidenib), an oral, targeted inhibitor for relapsed or refractory acute myeloid leukemia (AML) marketed by **Celgene Corp.** and **Agios Pharmaceuticals Inc.***(Also see "Celgene, Agios Ready For Enasidenib Launch After Early Approval" - Medtech Insight, 1 Aug, 2017.)*

The two August approvals put Abbott in the lead for the most original PMA approvals gained in 2017, including another *in vitro* diagnostic and **St. Jude Medical Inc.** MRI-conditional pacemaker devices approved earlier in the year. Four other companies have gained two original PMA approvals, each. (See Figure 1.)

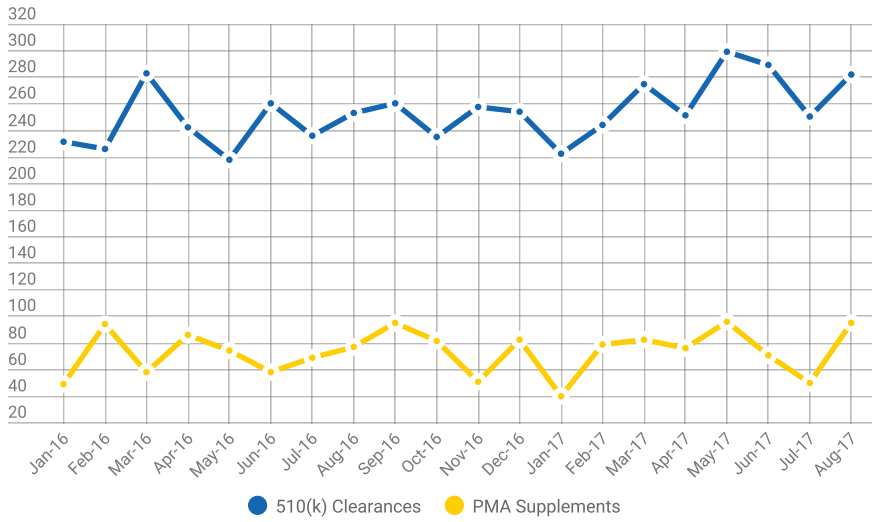
The other three original PMAs approved in August were **Bioventus Inc.**'s Durolane, a hyaluronic acid (HA) to treat knee osteoarthritis pain; **CR Bard Inc**.'s Lutonixdrug-coated balloon to treat stenotic lesions in arteriovenous (AV) dialysis fistulae who are facing kidney failure; and **Prollenium Medical Technologies Inc.**'s *Revanesse Ultra* dermal filler for facial wrinkle.

The five approvals bring the through-August total of original PMAs granted in 2017 to 31. FDA also approved two panel-track supplements and one *de novo* classification, rounding out the categories of

FIGURE 3

510(k) Clearances And PMA Supplements (Non-Panel Track)

Monthly trends for 510(k) clearances and non-panel-track PMA supplements, excluding 30-day notices.



*Source: **Medtech Insight**'s Approvals Tracker*

so-called "novel" device and indication approval pathways. (See Figure 2.) Since 2015, FDA has significantly upped its volume of novel approvals, and, in 2017, the agency is outpacing its recent-year performances, particularly due to strength in the original-PMA and *de novo* numbers. *(Also see "US Approvals Analysis: 2016 Another Record Year For FDA Novel Device Approvals" - Medtech Insight, 13 Jan, 2017.)*

FDA also cleared 282 510(k)s in August. Among notable clearances from last month:

- **Renovis Inc.**'s Tesera porous titanium interbody fusion systems, 3D-printed devices for posterior spine procedures;
- An expanded indication for **NxStage Medical Inc.**'s System One for solo home hemodialysis, without need for a care partner, during waking hours; and
- **Globus Medical Inc.**'s Excelsius GPS robotic guidance and navigation system for minimally invasive and open orthopedic and neurosurgical procedures.

Also in August, FDA approved 95 non-panel-track PMA supplements.

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CONTINUED FROM PAGE 1

linked to four major quality system subsystems: management controls, corrective and preventive action (CAPA), design controls, and production and process controls.

The technique was devised so investigators could inspect within a brisk three- to five-day window. That's a timeframe that investigators typically meet for foreign-based inspections where travel time is limited to a set number of consecutive days.

"FDA has extremely limited time when they're on a foreign inspection because they don't have endless money to let an investigator camp out in a foreign country. So, typically for a baseline inspection, you're talking only about four days in the foreign facility," Chase said.

But such a quick inspection turnaround doesn't usually translate to FDA audits that take place inside the US.

"So, rightfully so, the domestic firms are ticked off," Chase said. "They have a reason to complain about that, and they should complain about it."

That's where new inspection-specific provisions in FDARA come into play.

Under Sec. 702 of the law, "Improvements to Inspections Process for Device Establishments," FDA must give manufacturers "reasonable" advance notice of when an inspection will take place. Domestic companies currently receive a five-working-day notice, while overseas firms are given more leeway – they're contacted by the agency weeks in advance of an audit so international travel can be arranged, giving those firms more time to prepare.

Further, Sec. 702 says the agency must provide manufacturers with "a reasonable estimate of the timeframe" for an inspection. It also calls for FDA to establish a "standard timeframe" for domestic and foreign audits, specifying that inspections should be performed "over consecutive days."

The law gives FDA until February 2019 to write a draft guidance that lays out exactly how the agency will do that, along with other inspection-related provisions specified in Sec. 702.

Chase said FDARA's consecutive-day audit requirement might cause the agency to "tighten the reins domestically" on investigators that dip in and out of an inspection, causing it to be chopped up and spread over multiple weeks.

But she noted that implementing a "standard timeframe" to inspect both domestic and foreign firms might be a stretch for the agency.

"FDA could say, 'You want parity between foreign and domestic firms? OK, well, we can tell our staff that they only get four days in a foreign inspection, so now they only get four days in a domestic inspection,'" Chase said. "But what will be the consequence of some supervisor allowing investigators to spend only five days in a facility?"

That won't happen, she said, "because an investigator will say to their manager, 'Look, I have evidence of problems at this facility, but I legitimately need another two or three days to collect the evidence necessary in the domestic market to be able to say we have a serious problem here.' That investigator's manager will never say, 'Oh, no, sorry, can't do it,' because if somebody ends up dying and that happens on their watch, now they've got a bigger problem.

"The liability is too high to tell an investigator to essentially turn a blind eye because the foreign firms get only four days of inspection time and the domestic firms are annoyed because they get 20 audit days."

Despite the new inspection timeframe requirements, FDARA nevertheless gives the agency carte blanche to extend a facility's inspection time. Sec. 702 states that an audit can continue beyond given timeframe estimates if an investigator finds "a reason that more time is needed" to conduct the inspection.

"Not finishing an inspection because the investigator feels like there's a 'reason'

CLICK

Ricki Chase is the expert speaker for Medtech Insight's suite of educational **Compliance 360°** podcasts. Check out the first 9 here: http://bit.ly/2nMglqj

Implementing Sec. 702

Jeff Shuren, director of FDA's Center for Devices and Radiological Health, told *Medtech Insight*: "To implement Sec. 702, FDA can implement internal controls such as the revision of SOPs [including the Compliance Program Guidance Manual and Sec. 5.2 of the Investigations Operations Manual], tracking and reporting metrics related to time between inspection start and inspection end dates, training investigators on the importance of efficient inspections, and adopting successful practices used in foreign inspections at domestic sites."

Did You Know?

FDARA Secs. 701, 702 and 704 – which cover a range of inspection issues and tweaks the agency's approach to certificates to foreign governments – is a rewrite of US Senate bill S.404, introduced by Sens. Johnny Isakson, R-Ga., and Michael Bennet, D-Colo., in February.

S.404 complained that inspections of foreign device firms are "conducted more efficiently" than those for their US counterparts. *(Also see "New Bill Aims To Bring Consistency, Transparency To US FDA Inspections" - Medtech Insight, 16 Feb, 2017.)*

Like FDARA, S.404 called 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.

to stay is very ambiguous. So, who gets to say what the 'reason' is? What's the threshold for a 'reason'?" Chase said. "I just don't believe the language in this particular law is going to make much of a difference at all in the length of domestic inspections."

Chase maintains that the bulk of manufacturer complaints about inspections – including unpredictable, extended audit timetables – stem from poor investigator behavior.

"If you get down to the root cause [of troublesome inspection timeframes], oftentimes it's because investigators weren't behaving professionally, and they weren't operating in accordance with the Compliance Program Guidance Manual," she said, claiming that "90% of what FDARA is asking for" already exists at the agency, including policies and procedures that govern investigator behavior.

"The policies for employee behavior and employee conduct at inspections, and timeliness and communications – FDA already has those. That isn't new," Chase said. "So, the problem isn't getting FDA to write policies and procedures to govern these types of things; instead, the problem is getting FDA to enforce them internally.

"That's the problem, because if your staff doesn't follow the guidance, or the rules, or the [QSIT] inspection technique, and they're just doing their own thing, then it appears that you have no governing rules. But FDA does. It just doesn't always follow them."

FOREIGN INSPECTIONS: TOO SHORT?

But some in industry say it's difficult to comprehensively inspect a device-maker's quality system within an inspection window of five days or less, which is another reason why domestic audits can take longer to complete.

For example, former FDAer Tim Wells – now an industry consultant – said in an interview with *Medtech Insight* late last year that he would like to see the agency conduct fewer inspections, but schedule them to be twice as long.

If FDA "inspected for 10 days total, or if they had two auditors at the inspection, hell, they would get some good inspections done," he said at the time.

Coauthor of the Quality System Inspection Technique in the late 1990s, Wells said he no longer fully stands by the "quick" audit approach, pointing out that it can take investigators "half a day just to figure out where the bathrooms are, and to get a product overview and an understanding of the building, the layout plan, and all those things."

Wells says QSIT needs to be modernized, and he is working on an updated version that firms can use when they audit internally. *(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.)*

In an Aug. 29 email to *Medtech Insight*, CDRH Director Jeff Shuren was vague as to whether QSIT will be eventually revised.

Shuren wrote: "FDARA does not mandate that QSIT will be reviewed and/or modified. However, FDA is continually involved in process improvements related to how we conduct inspections."

When it comes to overseas inspections, a compressed schedule could actually put a foreign firm at a disadvantage, said Steve Niedelman, lead quality systems and compliance consultant at the law firm King & Spalding.

"One of the benefits FDA has with foreign inspections is the interpretation of imports under [21 US Code § 381], where there just needs to be an appearance of adulteration and misbranding to place a firm on import detention. And certainly, not having a compliant quality system is an adulteration charge," Niedelman told *MedtechInsight*.

Niedelman – a familiar face in the medical device arena – worked at FDA for 34 years in both its Office of Regulatory Affairs and Center for Devices and Radiological Health.

"A lot of foreign firms are on import detention based on those tight four-day quality system inspections, and therefore, it stops shipments into the United States for those products because of the agency's concern," he said. "So, the flexibility that the imports statute provides FDA gives the agency greater comfort in conducting these more condensed inspections overseas."

'IT'S NEVER GOING TO BE FAIR'

Consultant Chase agreed with Niedelman's assessment, noting that FDA's threshold for evidence is "very, very low" when performing a foreign inspection.

"In the domestic market, FDA essentially must prove beyond a reasonable doubt that a product is misbranded or has been rendered adulterated to take an action," Chase said. "But in the foreign market, FDA only needs the appearance of a violation" to place a company on import alert and refuse to let its products into the US.

Because of FDA's limited resources, "even if an investigator is like, 'Holy smokes, this place is a disaster, but it's in the middle of India and I only have four days,' they're going to collect as much evidence as possible in those four days, and it's probably going to be enough to put

the firm on import alert," she said.

But in the US, "FDA is not going to get a seizure warrant, and it's not going to get an injunction against a domestic firm unless it has put endless months, and sometimes endless years, of work into building a case to do that," Chase said. "So, the foreign threshold is very low. Instead of having to build a case of 20 examples of a domestic firm's deficiencies, an investigator really only needs to grab two or three from a foreign firm."

Chase said a requirement in FDARA Sec. 702 that asks FDA to provide for "uniform processes and standards" for domestic and foreign inspections is a congressional pipe dream.

Congress, through FDARA, "wants to compare apples to apples, and they can't do that because foreign firms have the luxury of not being subject to the FD&C Act – but of course with that 'luxury' comes the threshold of the importation law [21 US Code § 381]. If a foreign firm wants to get their product on the US market, it must comply because the mere appearance of noncompliance means the FDA won't let you do that," Chase said.

"That's the interesting part of this, about the 'uniform processes and standards' – about the parity between foreign and domestic – because FDA will not establish that parity," she said. "A domestic firm will never undergo the same type of inspection as a foreign firm because legally the threshold for evidence is different.

"So, it's not fair, and it's never going to be fair."

ENHANCED COMMUNICATIONS TARGETED

Better communications between manufacturers and FDA before, during and after an inspection is also a goal of FDARA under Sec. 702. In fact, the law directs the agency to create "standardized methods" for communicating with firms.

Using communications templates, FDA will have to tell a manufacturer in advance of its inspection the "type and nature" of the audit, and determine the facility's hours of operation.

Also before an inspection, FDA will notify the firm of documents that will be requested by investigators when they arrive onsite. While that directive looks good on paper for device-makers that want to be prepared, it won't be much of a change agent in how the agency operates inspections, consultant Chase argues.

That's because FDA will likely ask companies for very general documents in advance – ones that all firms probably have on hand already – and instruct investigators to ask for more specific documents during the inspection, in real time.

"FDA is always good at taking advantage of the fact that laws are written very vaguely. They'll write guidance for the staff or rules for the staff that meet the spirit of the law," Chase said.

"What FDA will do is say to firms, 'OK, we're required to tell you what you need to have ready for the inspection, so let me tell you what you need to have: validations, SOPs and your quality manual,'" she said. "That's all very vague, and it's everything that they already know that they're required to have by law anyway.

"So, I don't see where [an advance document request] is really going to put a lot of teeth into what FDA does. I don't see it changing what they do, because the law cannot be that prescriptive."

Sec. 702 also calls for "regular communications during the inspection … which may be recorded" – something that King & Spalding's Niedelman said won't necessarily be a big game-changer either.

"ORA for the longest time has prompted its investigators to share daily downloads as inspections progress to provide daily updates so there are no surprises at the end of the inspection when FDA-483 observations are unveiled," Niedelman said.

ORA is FDA's Office of Regulatory Affairs, which conducts all of the agency's field activities.

Historically, "by investigators providing those daily updates, firms have been able to make changes during inspections," Niedelman said, pointing out that FDA-483 inspection forms can be annotated by investigators to show that quality system corrections or changes took place while the audit was ongoing.

"I don't think that language in FDARA will provide any change to businesses, other than codifying the expectation that communications during inspections must happen," Niedelman said. " I don't see that as anything new."

FDA FEEDBACK ON CORRECTIVE ACTIONS

Perhaps more significantly, FDARA Sec. 702 creates an opportunity for manufac-

Risk-Based Inspections

FDARA Sec. 701 instructs FDA to develop a "risk-based schedule" for facility inspections. However, the agency has used a risk-based approach to determining which facilities to inspect since the mid-2000s. *(Also see "FDA's Risk-Based Approach To Facility Inspections Undergoing Refinements" - Medtech Insight, 1 Nov, 2008.)*

Because FDA "effectively uses risk-based scheduling now to determine which establishments to inspect, [FDARA] would help align the statute with current practice while allowing FDA to meet its statutory requirements," CDRH Director Shuren said.

What's new, though, is that FDARA says FDA should consider a device-maker's participation in international audit programs – such as the Medical Device Single Audit Program – when making inspection location decisions based on risk.

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. Firms must be audited to MDSAP by Jan. 1, 2019, if they want to sell product in Canada. *(Also see "'Perfect Storm' Arrives: Clock Ticking For Device Firms To Conform To ISO 13485, MDSAP, EU & ASEAN Regs" - Medtech Insight, 11 May, 2017.)*

AP Program Reauthorized

Meanwhile, FDARA Sec. 703 reauthorizes FDA's third-party accredited persons (AP) inspection program for another five years, until Oct. 1, 2022.

Under the little-used initiative, companies that make higher-risk class II and III devices sold domestically and overseas are permitted to hire agency-approved AP auditors to conduct FDA quality system inspections. *(Also see "Problems Still Abound For FDA's Accredited Persons Inspection Program" - Medtech Insight, 1 Nov, 2009.)*

"Although the accredited persons (AP) inspection program may have been underutilized, there have been some manufacturers who participate," CDRH Director Shuren wrote to *MedtechInsight*.

And FDARA did more than simply reauthorize the AP program, he noted.

Sec. 703 also "added authority to recognize organizations as accredited persons," Shuren wrote. "In order to use the expanded authority, the broader authorization in the section was renewed. As a result, FDA will be able to leverage inspections conducted under the Medical Device Single Audit Program."

The AP program, which began in the early 2000s, allows manufacturers that are subject to frequent FDA and foreign inspections to undergo both types of audits during a single visit – a concept very much like MDSAP.

Export Certificates Addressed By FDARA

FDARA Sec. 704 allows device-makers to keep their certificates to foreign governments (CFGs) if the firms can prove to FDA that it has a plan to correct problems found during a facility inspection.

Such certificates allow companies to export products overseas. Rarely does the agency pull a firm's certificate. In fact, less than 1% of CFG requests – 249 out of 27,092 – were withheld from manufacturers in fiscal years 2014-2016, FDA told *Medtech Insight*.

If a CFG is yanked, it usually happens after a corporate warning letter is issued. Corporate letters are an enforcement tool intended to force top company executives at large firms to address systemic quality systems at all of their manufacturing facilities.

Sec. 704 also looks "to improve transparency regarding why CFGs are denied, and to improve the ability of the agency to issue a CFG when a company requests a CFG for a product manufactured outside the US and shipped outside the US, without having to first ship the product to the US," CDRH Director Shuren added.

turers to request informal feedback on proposed corrective actions to address deficiencies fingered by investigators, Akin Gump attorneys Nathan Brown and Howard Sklamberg wrote in a recent *Medtech Insight* guest column. *(Also see "World of Change Coming For Device Manufacturers: Developments In FDA And International Inspections" - Medtech Insight, 25 Aug, 2017.)*

The lawyers pointed out that under FDARA, "if an FDA inspections report contains observations and related corrective actions that implicate a public health priority or an emerging safety issue, or would involve systemic or major undertakings by the establishment, then FDA must respond to a request for 'nonbinding' feedback on the proposed actions within 45 days."

Brown, a former special assistant to the FDA chief counsel, and Sklamberg, a former deputy commissioner for global regulatory operations and policy at the agency, wrote that the provision "addresses concerns by device sponsors that they often undertake costly or complex corrective actions without any clear signal from FDA that their actions will fully address the agency's concerns."

In a separate interview with *Medtech Insight*, Brown elaborated on why FDARA's FDA feedback requirement is a win for device-makers.

"Companies are not always clear about what types of corrective actions would be sufficient to address FDA's observations," he said. "So, given the breadth of medical technology and the fact that it is changing rapidly, there can be situations in which a company very much wants to address an observation as quickly as possible, but may not be confident that whatever changes they invest in will be ones that FDA subsequently agrees were what the agency was looking for."

It's important for firms to get that quick feedback so they can save time and money, Brown said. Nevertheless, he doesn't believe the feedback mechanism will be routinely used by manufacturers.

"By-and-large, companies will know what they need to do to address typical observations," Brown said.

"But I think there are also situations in which an observation may raise new issues or may implicate a scope of changes that are time-consuming and costly to undertake, and may involve making systemic changes that cross different plants," he said. "And before undertaking those, I think there are situations when companies would prefer some opportunity for informal dialogue with FDA that they're on the right track, and given that FDA may not come back to reinspect a facility for quite some time, they would prefer to know that what they're proposing to do has a high degree of likelihood of addressing the concern that FDA had."

Brown urged firms to think proactively when it comes to communicating with the agency.

Device-makers should "take advantage

of the increased opportunity to have an open dialogue with FDA, both at the front end of an inspection and during the inspection, if there are any questions or concerns that are arising about the inspection itself, and then afterwards, if there are issues that arise to the level of potentially benefiting from dialogue, an opportunity for feedback," he said.

SHUREN: PROGRAM ALIGNMENT COMPLEMENTS FDARA PROVISIONS

FDARA's inspection-related provisions should get a leg up because of FDA's "program alignment" inspection scheme, device center Director Shuren says.

Under program alignment, which began in May, inspections performed by FDA are structured along commodity-specific product lines to make audits more predictable and consistent for investigators and manufacturers. *(Also see "'Program Alignment' Falls Into Place: Everything You Need To Know About US FDA's New Inspectional Approach" - Medtech Insight, 8 May, 2017.)*

"Through program alignment efforts, FDA started centralizing site selection and started applying the foreign risk-based device-site selection model to domestic site selection, which aligns with FDARA's Sec. 701," the provision directing the agency to develop a risk-based inspections schedule, Shuren wrote in a Sept. 5 email to *MedtechInsight*.

And, "with regards to Sec. 702 on improving inspections: Prior to May 2017, CDRH interacted with 19 domestic districts and over 500 investigators who performed one or more device establishment inspection. Now there are three ORA domestic medical device divisions with approximately 150 dedicated medical device investigators," he wrote. "Through program alignment efforts, CDRH and ORA have established and provide device program-specific training."

Akin Gump attorney Brown agrees that FDARA and program alignment "are very complementary."

"FDA – and ORA in particular – has put a lot of time and thought into program alignment, and that is primarily organizational, but the rest of that is to have inspection cadres that are more specialized for each product area," he said.

"So, having a dedicated device inspection cadre that's used to dealing with device facilities on an ongoing basis facilitates this greater level of dialogue and predictability that is contemplated by the FDARA provisions," Brown added.

As a device-specific inspections cadre "is developed – which will be dedicated to evaluating the quality systems expectations for devices and will be ever more familiar with the agency's responses to particular quality systems issues – those investigators will be more equipped to engage in meaningful dialogue with a device establishment during an inspection, and the agency as a whole will in turn be better positioned to provide feedback to establishments that are working to respond effectively to inspections observations," he said.

"Moreover, because investigators' supervisors will also be dedicated device specialists, there will be enhanced vertical coordination within ORA, and horizontal coordination with CDRH, allowing for quicker and more consistent resolution of challenging issues," Brown explained.

"In short, program alignment makes it much more likely that the FDARA provisions will be successful."

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Gottlieb Wants More Systematic Updates Of Regulations

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US FDA Commissioner Scott Gottlieb says he wants to see a "systematic process" reviewing agency regulations to determine if they should be updated or withdrawn.

Last week, FDA issued notices in the federal register asking stakeholders for input on what regulations should be updated or pulled. *(Also see "US FDA To Public: Help Us Streamline Our Regs" - Medtech Insight, 7 Sep, 2017.)* The notice is in response to multiple executive orders from President Trump, including one from earlier this year telling federal agencies they are only allowed to issue a new regulation for every two that they erase from the books.

Responding to a question from *Medtech Insight* at the 2017 RAPS Regulatory Convergence Conference in National Harbor, Md., Gottlieb said the agency is mostly focused on looking to identify rules that need to be modified because they are out of date, rather than necessarily finding rules that should be dropped completely from the books.

The commissioner says the agency has sporadically addressed this type of overarching regulatory reform, but he would like to see a more predictable process going forward.

"This is an effort to try to look at not just which regulations might need to be addressed because they're outdated but also ask the question whether or not we can get in place a systematic process going forward as a regulatory agency to do this on a regular basis," he said. "FDA has undergone this exercise a number of times in its recent history, but I think rather than sort of periodically taking on this kind of an exercise, I'd like us to arrive at a more systematic process where we're doing this on a more continual basis and asking this question because sometimes we don't do that."

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LISTEN

Listen to Gottlieb's full response online at RAPS at http://bit.ly/2f9qddq.

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