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US APPROVALS ANALYSIS:

2016 Another Record Year For FDA Novel Device Approvals

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2016 was another historically productive year in US FDA approvals of novel devices or major new indications.

The agency approved a total of 91 original PMAs, panel-track PMA supplements and *de novo* classifications in 2016, according to an analysis by *Medtech Insight*. This is highest number of approvals in these novel device/indication pathways since the device user-fee program launched in 2002, breaking a previous record of 79 novel device approvals set in 2015. Between 2001 and 2014, the average approval total combining these three submission pathways was about 48.

Original PMAs, which are required to bring new, high-risk devices to the US market, actually dropped a bit from 43 approvals in 2015 to 39 this past year. But panel-track supplement approvals experienced what was, at least, a 16-year high in 2016, with 26 approvals last year, up from the previous high of 18 in 2015. These types of supplements are required to market new indications or major design or performance changes that require substantial clinical data for high-risk devices.

Meanwhile, there were 26 *de novo* classifications in 2016, just shy of the user-fee-era record of 28 in 2014, and well above the single-digit annual numbers that were common from 2000-2010.

Non-panel-track PMA supplement approvals (not including 30-day notices) also increased in 2016, up from 791 in 2015 to 874 last year.

But 510(k) clearances were a bit down in 2016. The agency cleared 2,956 510(k) s last year, compared to 3,050 in 2015 and 3,198 in 2014.

BEHIND THE NUMBERS

There are several factors driving the 2016 totals. The most clear-cut explanation is for *de novos*. There was a clear upswing in *de novo* submissions and classifications after Congress changed the law in FY 2013 to allow a "direct" *de novo* route that no longer forced companies to first be rejected in the 510(k) process.

FDA in recent years has encouraged greater use of the *de novo* process to establish appropriate regulation of certain product categories. Most recently, for example, the agency's final guidance on medical device accessories, issued in the final days of 2016, urges firms to use the process to reach the proper risk

ANALYZE
Check out our analysis of approval trends outside of the US (p. 6) and our infographic for all 2016 medical device approvals (p. 5).

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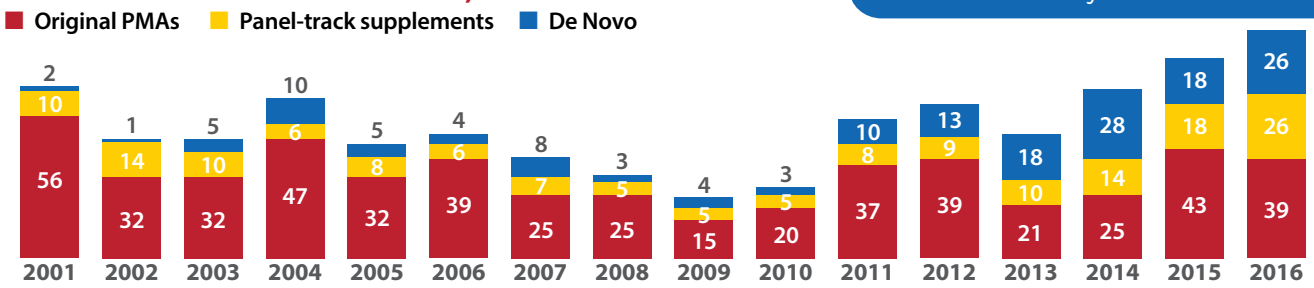
technology that enables surgeons to view a patient's external and internal anatomy in real time during minimally invasive spine surgery.

POLICY & REGULATION

Medical Device Approvals 2016

2016 was a record year for novel device approvals from US FDA, but 510(k) clearances were down slightly. Outside the US, the number of CE marks recorded on *Medtech Insight*'s Approvals Tracker was nearly flat with 2015.

NOVEL FDA DEVICE APPROVALS, 2001-2016



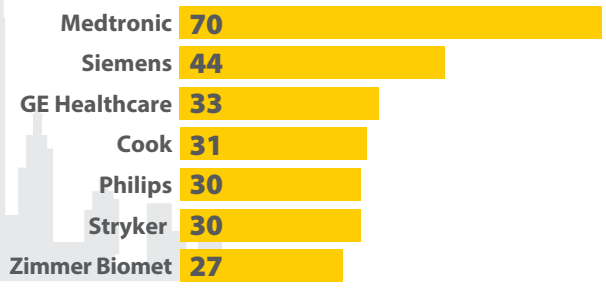
TOP COMPANIES

MOST ORIGINAL PMA, PANEL-TRACK, *DE NOVO* APPROVALS, 2016

- 7 Medtronic
- 7 Roche
- 5 Abbott Laboratories
- 4 Boston Scientific
- 4 Edwards Lifesciences
- 3 Alcon

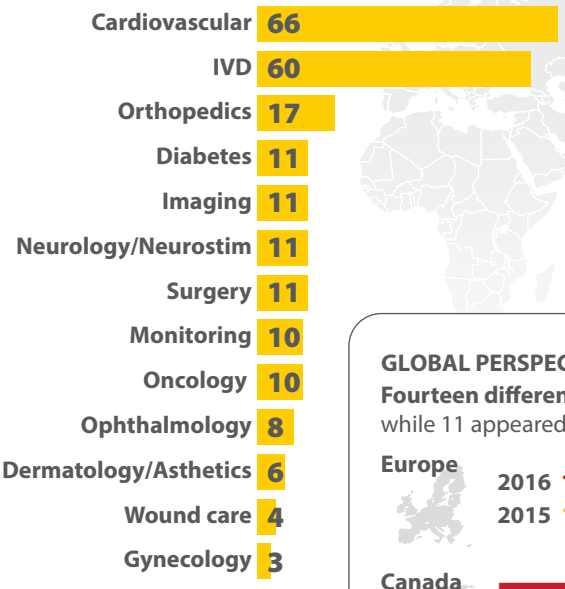
MOST 510(K) CLEARANCES, 2016

There were 2,956 510(k)s cleared last year, down from 3,050 in 2015.



NON-US APPROVALS

TOP DEVICE TYPES



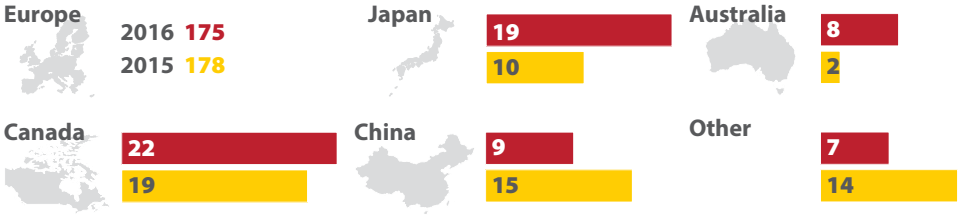
Medtech Insight's Approvals Tracker https://medtech.pharmamedtechbi.com/datasets/approvals

TOP COMPANIES

- 10 Medtronic
- 10 St. Jude Medical
- 6 Biotronik
- 6 Edwards Lifesciences
- 5 Abbott
- 4 Boston Scientific
- 4 Roche

GLOBAL PERSPECTIVE 2016 VS 2015

Fourteen different territories were represented on the 2015 Non-US approvals list, while 11 appeared in 2016.



CONTINUED FROM PAGE 1

classification for devices that "support, supplement or augment" a parent device. And anticipated growth of the program is reflected in the MDUFA IV user-fee agreement, which is expected to go before Congress this year and includes for the first time targeted user-fee and performance goals for *de novo* submissions.

FDA says reforms it has advanced over the past five years or so, including more interactive reviews, better efforts to ensure submissions are complete soon after submission and improvements to the clinical-trial approval process, are a major factor in driving up submissions and speeding up reviews of PMAs.

Submission volumes of original PMAs and panel-track supplements jumped up markedly in fiscal years 2015 and 2016, with 72 applications received by FDA in each of those years, compared to 45 and 43 submissions in FYs 2013 and 2014, respectively. Also, total times from submission to FDA decision appear to be dropping for PMAs.

Meanwhile, the most recently available FDA data suggests 510(k) clearance decision times have been inching back up, after a decline in FY 2013, paralleling the small drop in clearance totals.

ACTIVE DECEMBER

The end-of-year holidays certainly did not slow 2016 approval activity. In December, FDA approved three original PMA approvals, four panel-track supplements and six *de novo* classifications (the highest monthly total for the year for *de novos*).

Roche gained two of these December approvals for its *Elecsys* line of diagnostics, including an original PMA approval for the *Elecsys HBsAg II* hepatitis b serum and plasma assay for adult and pediatric use, and a *de novo* go-ahead for the *Elecsys AMH CalSet PreciControl* testing for the anti-Mullerian Hormone to assess the ovarian reserve.

Diabetes devices accounted for two linked novel-pathway approvals last month. **Dexcom Inc.** gained panel-track expanded approval for its *G5* continuous glucose monitor in patients as young as two years old, and Johnson & Johnson/Animas gained approval for the *OneTouch Vibe Plus* insulin pump, which is integrated with the G5 CGM, in the same patient population.

Other firms gaining novel-pathway approvals in December include **Cook Medical Inc.** (expanded indication for the *Zilver PTX* drug-eluting peripheral stent), **QMed Inc.** (*Restylane Refyne* and *Restylane Defyne* dermal fillers) and Prescient Surgical (*CleanCision* wound retraction and protection system).

TOP COMPANIES

One measure of a company's regulatory and R&D productivity is the number of approvals and/or clearances it gets through FDA. On this measure, **Medtronic PLC**, particularly in the wake of its 2015 acquisition of Covidien, is a dominant player, both in higher-margin PMA-type devices and potentially more commodity 510(k) products. The firm had the most novel-device approvals (PMA, panel-track supplement and *de novo*) and 510(k) clearances in 2016, as it did in 2015.

For novel device approvals, Roche matched Medtronic this year. Both firms had seven such approvals in 2016. For Medtronic, that included cardiovascular, diabetes and orthopedic devices. Roche gained marketing go-aheads for multiple cancer companion diagnostics, as well as the two non-cancer clinical assays mentioned above.

Abbott Laboratories Inc. was not far behind with five approvals. Abbott closed its approximately $25bn acquisition of **St. Jude Medical Inc.** Jan. 4. Adding St. Jude's two 2016 novel-pathway approvals to the total, would even it up with Medtronic and Roche with seven. However, two of Abbott's panel-track supplement approvals in 2016 came from the firm's AMO ophthalmic division, which the company is selling off to J&J.

For 510(k)s, Medtronic was way out ahead with 70 clearances recorded in 2016, though that fell short of the 83 clearances it achieved in 2015. **Siemens AG**, **GE Healthcare** and Cook Medical were other firms near the top on 510(k) clearances last year.

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OUS APPROVALS ANALYSIS:

Slow Finish To 2016, But Still Ahead Of 2015

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2016 started on pace for a big year of medical device approvals outside the US, but the pace peaked in the summer and tapered-off at the end of the year, *Medtech Insight*'s Approvals Tracker shows. In December there were just eight CE marks – by far the lowest number of any month in 2016 – and three approvals from outside the US or Europe.

Nevertheless, the total of 240 approvals from outside the US, including 175 CE Marks from Europe, beat 2015's total by two. The biggest increase from 2015's totals were from Japan, with 19 approvals versus 10, and Australia, with 10 compared to two. (See Figure 1)

Beyond Europe and the US, 10 different countries are represented on the Approvals Tracker in 2016, compared to 13 in 2015. The top four beyond Europe were Canada, Australia, Japan, and China.

Medtronic PLC and **St. Jude Medical Inc.** both announced 10 non-US product approvals in 2016, tying for the most. But if St. Jude is counted with **Abbott Laboratories Inc.** – which completed the $25bn acquisition of St. Jude on Jan. 4, 2017 – Abbott finished the year with 15 non-US approvals,

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Go only to http://bit.ly/29QApYR for sortable and searchable tables of all 2016 US and non-US approvals and clearances.

FIGURE 1

December 2016 Non-US Approvals

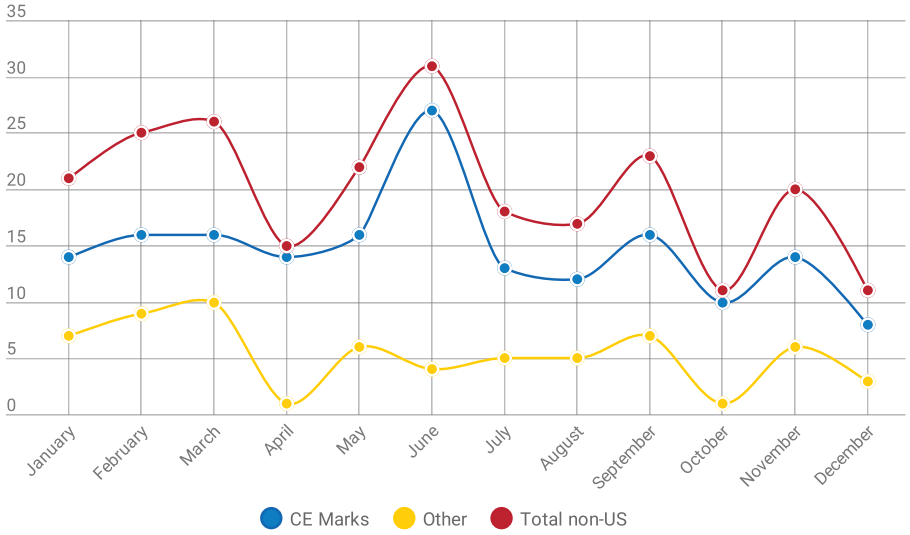

FIGURE 2

December 2016 Non-US Approvals By Product Category

PRODUCT CATEGORY	NUMBER
Cardiovascular	2
Diabetes	1
Imaging	1
Intravenous	1
In Vitro Diagnostic	2
Neurostim	1
Orthopedic	2
Wound Care	1
TOTAL	11

making it the US company with the most approvals outside its domestic market.

With the addition of St. Jude, Abbott will likely continue to lead the non-US approvals table most months and years because it has a broad portfolio in both cardiovascular and in vitro diagnostics. By far, the top categories for 2016 non-US approvals were these two very categories, with 66 non-US approvals for cardiovascular devices and 60 for in-vitro diagnostics. The next biggest category was orthopedics with 17. No other category had more than 11. (See Figure 2)

The rapid iteration of new cardiovascular and IVD products is also reflected in the rest of the table of companies with the most non-US approvals in 2016. In addition to St. Jude, Abbott, and Medtronic, the only other companies with more than three non-US approvals in 2016 were the major cardiovascular device companies – **Edwards Lifesciences Corp., Boston Scientific Corp., Biotronik SE & Co. KG** – and **Roche**, Abbott's main rival in the IVD space.

DECEMBER DIVE

IVDs and cardiovascular devices were the most populous categories in December, but with only two approvals each. (See Figure 2)

Medtronic scored both cardiovascular approvals, one in Japan and the other in Europe. The Japanese approval was for its self-expanding *CoreValve Evolut R* transcatheter aortic valve, along with the *EnVeo R* delivery system, based on robust data from the CoreValve U.S. Pivotal and CE Mark clinical trials. The low-profile (14 Fr, less than a 0.5 in diameter) CoreValve Evolut R is the successor to the CoreValve system, which was became first self-expanding TAVR system launched in Japan in 2015. The launch in Japan includes the 26mm and 29mm valve sizes with extended sealing skirts to further promote valve sealing at the annulus. Including these larger diameters in addition to the 23mm system will probably be important for staying competitive in the Japan TAVR space. Medtronic initially launched CoreValve Evolut R in the US without the 26mm or 29mm, and found that it was at a major disadvantage to Edward's *Sapien 3* TAVR system without the larger diameters.

Medtronic also scored the other non-US cardiovascular approval in December with the Dec. 6 CE Mark for a new indication for the *Endurant II* and *Endurant IIs* abdominal aortic aneurysm stent graft. The approval covers implanting the Endurant endoprosthesis with the ChEVAR procedure, a so-called "parallel graft chimney" technique with balloon-expandable covered stents and a standard aortic stent graft. This approach is especially useful for treating patients with complex aneurysms with a short aortic neck (≥2mm). Previously, the Endurant systems were approved for treating patients with an aortic neck at least 10mm in length.

The two IVD approvals were CE Marks for **Biocartis NV**'s *Idylla* NRAS-BRAF mutation test and **HiberGene Diagnostics Ltd.**'s *HG* C difficile test.

Belgium-based Biocartis says that the test for the NRAS-BRAF mutations, alone with its Idylla KRAS mutation test that already has a CE Mark, will allow Biocartis to offer a complete high-sensitivity single-biopsy test for metastatic colorectal cancers on its Idylla formalin-fixed paraffin embedded tumor molecular diagnostics platform, consistent with the most recent clinical guidelines from the American Society of Clinical Oncology and the European Society for Medical Oncology. The NRAS test detects 18 mutations and the BRAF test looks for five mutations so, along with the KRAS test that detects 21 mutations, the Biocartis colorectal cancer test offering now allows simultaneous detection of 44 "clinically actionable" colorectal cancer targets.

HiberGene announced the CE Mark and launch of its HG C difficile test for accurate detection of Clostridium difficile bacteria from stool samples in under 60 minutes. C. difficile is the major cause of hospital-acquired diarrhea, which can be fatal in some vulnerable patients and highly infectious despite modern cleaning methods, the company says. This is the third test HiberGene's has launched, along with Meningococcus and Group B Streptococcus tests.

VC DEALS ANALYSIS:

2016 Bucks The Trend As Investment Dollars Dip

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It had all started so well: 2016 had stormed ahead when the year began, bagging more medtech venture financing dollars – month after month – than 2015. But it ran out of steam just as it entered the second half of the year and eventually lagged behind, unable to catch up despite a last-minute surge in December. In the end, 2016 saw a decline in both deal value and volume from the previous year, clocking up 263 financing rounds of at least $1m and raking in over $5.135bn in total. Compared to 2015, this represents an 11% drop in volume and a 2% dip in deal value. (See Figures 1 and 2)

The shortfall could reflect the general lackluster exit markets in 2016: medtech IPO volume, already down in 2015 from the previous year, took a further nose dive in 2016 with only 14 completed IPOs (vs 27 in 2015). Meanwhile, M&A activity also slowed down last year, with M&A deal volume plunging from 237 in 2015 to 174, as tracked by *Medtech Insight*.

This gloomy exit outlook could have made investors less keen to invest in the sector, thus pushing down total volume and, subsequently, value in 2016

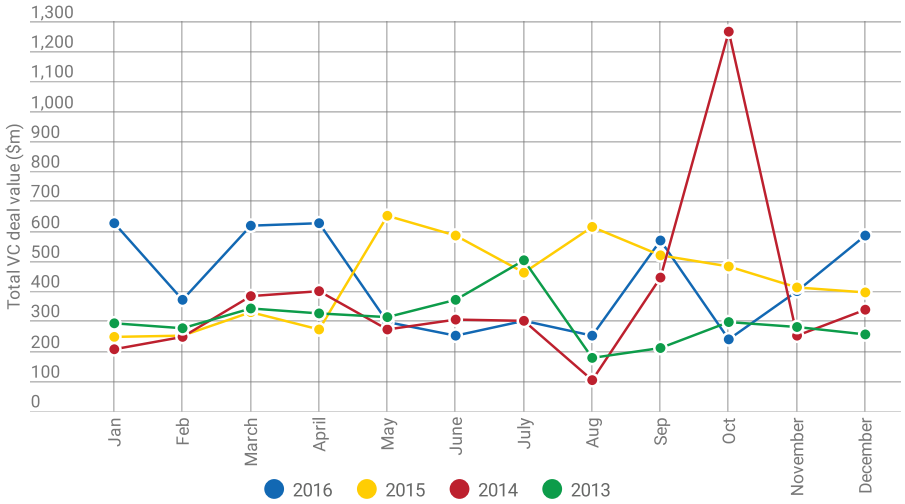
FEWER BUT MORE GENEROUS INVESTORS

That said, when investors did find something they wanted to invest in, they did not hold back. While 2016 did not have many deals in the lower end of the value range, it beat the past three years in terms of bigger buck financings. 2016 recorded 15 financing rounds that fell in $40-50m range, over twice as many as 2015, 2014 and 2013. Last year also saw 15 financing rounds that raised more than $50m, outperforming 2015 which had 14 deals in this range, 2014 which had 12 and significantly overshooting 2013's six deals. (See Figure 3).

Of the 15 deals that raised over $50m in 2016, six were $100m-plus rounds. Two of these nine-figure deals came from

FIGURE 1

Total amount raised by month, 2013-2016



Source: Medtech Insight

FIGURE 2

Total amount raised by year ($m), 2013-2016

2016 broke the VC financing bull run seen in the last three years

	2013	2014	2015	2016
H1 2016 total	1,927.85	1,812.8	2,340.6	2,787.4
H2 2016 total	1,727.0	2,706.9	2,889.0	2,348.5
FY 2016	3,654.8	4,519.7	5,229.5	**5,135.9**

Source: Medtech Insight

December alone. (See Figure 4). The final month of 2016 was a typical example of quality over quantity, where the low volume (19 deals vs 23 deals in Nov vs 31 deals in Dec 2015) was more than compensated by the $126m raised by UK gene sequencing specialist Oxford Nanopore Technologies and the $206m raised by drug deliver firm Intarcia Therapeutics.

The biggest round of the year was a $220m Series B raised by Human Longevity, the California company co-founded and headed by genomics veteran Craig Venter. The firm's mission is to build the largest and most comprehensive database of whole genome, phenotype and clinical data and its businesses include Health Nucleus, which offers health evaluations of patients by interpreting their genome and devising a health plan based on this information. (See infographic)

Among Human Longevity's shareholders is next-generation sequencing (NGS) specialist Illumina, which has been a

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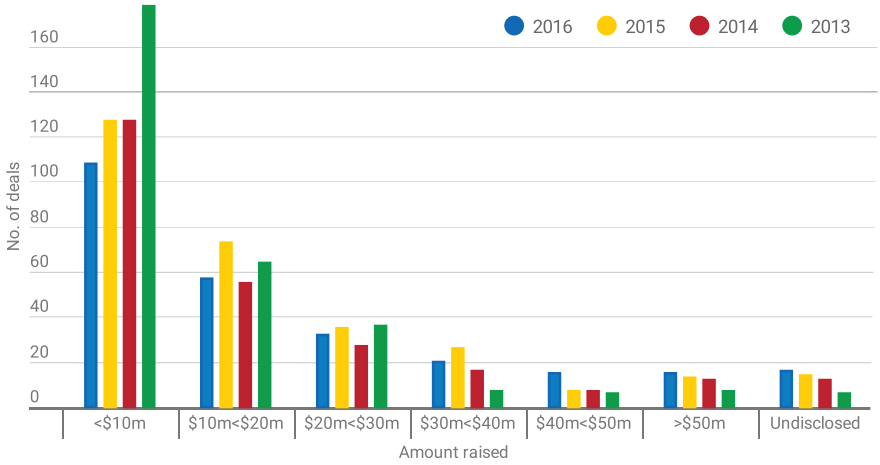
For more details about VC deals, go to Medtech Insight's VC deal tracker: https://medtech.pharmamedtechbi.com/datasets/vc-funding]

FIGURE 3

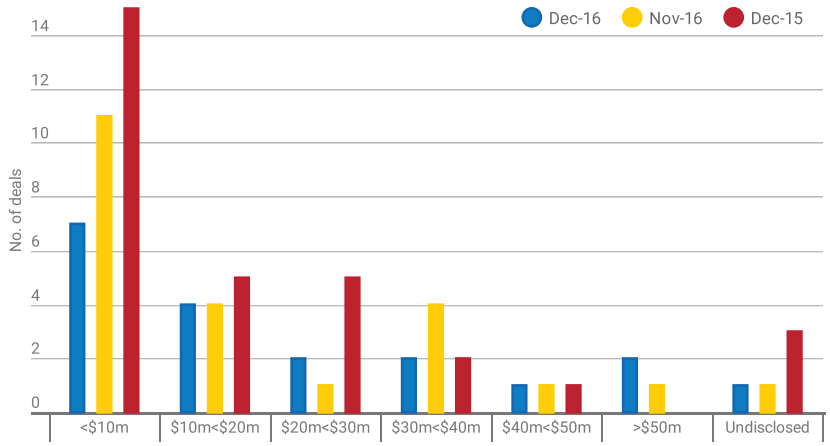
No of deals by value range, 2013-2016



Source: Medtech Insight

FIGURE 4

No. of deals by value range, Dec 2016



Source: Medtech Insight

particularly busy investor in 2016. Aside from Craig Venter's venture, Illumina is a major shareholder in its genomics spin-out, Grail, which raised $100m in its first financing round, the biggest series A of the year. (See Figure 5).

Grail will use Illumina's NGS technology to develop a simple, all-inclusive blood test to screen asymptomatic patients for early-stage cancer. The test would measure directly circulating nucleic acids originating from the cancer cells, and Illumina believes it could provide a technology that would enable economical sequencing and achieve the high levels of sensitivity and specificity required for a robust cancer screening tool. In addition to Illumina, others who are betting on Grail include Arch Venture Partners, Bezos Expeditions, Bill Gates and Sutter Hill Ventures.

Not content with being top of the A-listers in 2016, Illumina announced on Jan. 5 that Grail is seeking to raise an ambitious $1bn in its Series B from unnamed private and strategic investors and to close the round by the end of the first quarter. The proceeds will be used to continue development of Grail's pan-cancer test and fund trials to validate the technology, as well as to repurchase a portion of Illumina's stake

A billion dollars is a considerable amount for a venture investment – even by the standards of the biotech sector, medtech's more monied cousin – and Grail's ambitious move is testimony to its confidence that investors' attraction to the genomics space will continue into 2017.

DRUG DELIVERY BIGGEST LEAP

Indeed, IVD retained its crown from last year as the most popular sector for investment in 2016, with 59 financing transactions in total. Of these, nearly a third involve companies developing genomic-related technologies.

Cardiology/Vascular technologies remained the second most popular sector, although there seems to be renewed interest in Orthopedics, which went up one place from its 2015 ranking to number 3 (see Figure 6).

The sector that made the biggest leap in the investment popularity stakes was Drug Delivery, which went up from number 14 to number 5 this year. Some of the fundraisings in this area were the more sizeable ones seen this year too; one company to point out is Intarcia Therapeutics, mentioned earlier in this article, that closed two massive tranches of growth equity in 2016. In September, it raised $215m, the first tranche of a series E and in December, it closed a second tranche of $206m. The company – which counts Bill and Melinda Gates among its backers – is developing drug delivery devices based on its Medici platform. This consists of a matchstick-sized mini-pumps that can store highly potent small molecules at human body temperature for three years or more and deliver the medication continuously. As drug companies seek a way for new agents to be delivered more effectively – and conveniently – to patients, companies like Intarcia will likely see increasing interest from both institutional and strategic investors.

SOME CRYSTAL BALL GAZING

Looking ahead, how will the medtech venture investment landscape shape up in 2017?

Genomics, within IVD, will keep attracting interest, as would the usual suspects in cardiology/vascular and orthopedics (likely spine, where there is most inno-

2016 VC Investing In Medtech

2015 had ended on a high note for start-ups and SMEs seeking venture investment and **2016** began to look like this positive trend might continue. However, in spite of a bullish start and a few nine-figure rounds, activity slowed down in the latter half of the year. **Here are the key figures on the investment climate in 2016.**

TOTAL VENTURE DOLLARS RAISED

2016	2015
$5136m	$5230m

TOTAL DEAL VOLUME

2016	2015
263	295

BIGGEST SINGLE VC FUNDING ROUND

2016

$220m

HUMAN LONGEVITY (IVD/GENOMICS)

2015

$200m

MEVION MEDICAL SYSTEMS (CANCER MANAGEMENT)

$200m

NANTHEALTH (IVD/GENOMICS)

NO. OF ROUNDS OVER $100M

2016	2015
6	7

BIGGEST SERIES A ROUND

$100m

GRAIL (IVD/GENOMICS)

FIVE MOST POPULAR INVESTMENT AREAS

(by deal volume)

1. **IVD** (59)
2. **CARDIOLOGY/ VASCULAR** (31)
3. **ORTHOPEDICS** (19)
4. **DIGITAL HEALTH** (14)
5. **DRUG DELIVERY** (13)

For a full analysis of venture financing deals in 2016 and data on all the transactions tracked by Medtech Insight, click here or go to www.medtechinsight.com

FIGURE 6

RANK 2016 (2015)	PRODUCT SECTOR	NO. OF DEALS
1 (1)	IVD	59
2 (2)	Cardiology/Vascular	31
3 (4)	Orthopedics	19
4 (10)	Digital health	14
5 (14)	Drug delivery	13
6 (8)	Patient monitoring	12
7 (3)	Surgery	11
8 (12)	Diabetes management	11
9 (6)	Ophthalmology	11
10 (4)	Imaging	9

Source: Medtech Insight

vation). The rise of digitally-enable technologies and digital health will continue.

If Grail does succeed in closing its $1bn round before its first-quarter deadline, the year's total deal value would get a much welcomed early boost. Intarcia is also looking to close its third and final tranche – which would most likely be as sizeable as its previous two tranches – and this could give 2017 a good head-start. So it could well be that 2016's dip is just a one-off and deal value would go up once again in 2017. However, deal volume could remain modest, as investors decide to invest big but in a smaller, choice selection of companies.

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Do Hill-Rom, PerkinElmer, Integra Deals Signal 2017 M&A Acceleration?

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Following a slowdown in M&A activity lasts year, 2017 is off to a fast start with three medtech M&A deals in the space of a week – **Hill-Rom Holdings Inc.** is acquiring **Mortara Instrument Inc.**, **Integra LifeSciences** is acquiring **Derma Sciences Inc.**, and **PerkinElmer Inc.** will buy **Tulip Diagnostics Private LTD**.

2016 had fewer medtech mergers overall and fewer billion-dollar acquisitions than 2015 or 2014, but there were 14 deals in December, and including two other deals announced at the start of the month, January has already pocketed five deals, suggesting that M&A activity in the sector may be accelerating.

Three of the deals in January were announced during the JP Morgan Health Care conference in San Francisco, the largest health-care investment symposium on the calendar, with presentations of more than 450 medical device, drug, biotech and other health-care companies, and more than 9,000 investors in attendance, according to JP Morgan.

On Jan. 10, Hill-Rom announced a definitive agreement to acquire privately held Mortara Instrument for $330m in cash. Milwaukee-based Mortara recorded about $115m in revenue in 2015 and has been growing around 4% annually, according to Hill-Rom, which expects 2017 earnings from the Mortara products to be around $25m, and for the merger to eventually yield $10m annually in synergies.

Hill-Rom believes Mortara's diagnostic cardiology devices – including products for electrocardiography, cardiac stress exercise, Holter monitoring, ambulatory blood pressure monitoring, cardiac and pulmonary rehabilitation, and multi-parameter patient monitoring – will be a good fit with the instrument business Hill-Rom created when it acquired **Welch Allyn Inc.** in 2015.

Welch Allyn and Mortara "enhance our offering to our [integrated delivery network (IDN)] customers, as well as nonacute customers," Hill-Rom CEO John Greisch said at the JP Morgan meeting on Jan. 10.

"Leveraging our US sales channel, leveraging our US IDN relationships, leveraging our international footprint, we expect to be able to enhance the growth profile that Mortara has been able to achieve as an independent company," Greisch explained. "One of the strengths of Mortara is also the connectivity that they've got with many of the [electronic medical record] companies. We've got that also within Welch Allyn, so the combination of the connectivity capabilities together with our ability to leverage our brand equity of IDNs and our international footprints, we're really excited about this addition to the portfolio."

Greisch added that Hill-Rom will be able to record a $40m tax benefit from the deal. "We think we've got a very attractive purchase price for this business," he said. "It also is going to be accretive immediately to our adjusted earnings, accretive to our gross margins, accretive to our operating margins and has a significant synergy opportunity, again as a result of being able to leverage the Welch Allyn platform that we acquired over 15 to 16 months ago."

PERKINELMER EXPANDS INDIAN PRESENCE WITH TULIP

On Jan. 6, Boston-based lab-services and diagnostics company PerkinElmer announced the acquisition of Goa, India-based Tulip Diagnostics for an undisclosed figure.

Tulip is one of India's largest provider of *in vitro* diagnostics, reagents, kits and instruments for infectious diseases, and has manufacturing facilities in Goa and Uttarakhand, plus 12 offices that serve more than 30,000 customers and a thousand distributors throughout India.

At the JP Morgan conference, PerkinElmer CEO Robert Friel pointed out that infectious diseases account for about 25% PerkinElmer's diagnostic's sales, especially in China and India. He added: "You're seeing … a lot of the emerging market governments and health-care officials really looking more closely at the blood supply – which, obviously, plays into some of our capabilities there – but also just making sure that we're developing again safe, reliable, cost-effective tests in the infectious disease area, [which] plays into one of our strengths."

The deal for Tulip comes less than a month after PerkinElmer agreed to sell its medical imaging business to **Varian Medical Systems Inc.**, and represents the company's ongoing effort to focus on serving the diagnostics and research markets.

INTEGRA INCREASES STAKE IN REGENERATIVE TECHNOLOGY WITH DERMA

Integra LifeSciences has agreed to pay about $200m, or $7 per share, for fellow New Jersey-based firm Derma Sciences, which develops and sells regenerative products derived from placental/birth tissues, the companies announced Jan. 10.

At the JP Morgan meeting, Integra CEO Peter Adruini explained that Derma fits into Integra's "'3 x 3 strategy.' This strategy is based on three product families – engineered collagen matrix, acellular dermal matrix products and human amniotic tissue products – and three sales channels/customer groups – inpatient, outpatient and enterprise. *Omnigraft* and *PriMatrix* fill the engineered collagen matrix and acellular dermal matrix roles, respectively, and now Derma Sciences brings the amniotic tissue products to Integra's portfolio," Adruini explained. "So, we're quite excited about what that means for us in growth in the outpatient wound-care market."

In addition to traditional wound dressings, Derma's current products include TCC-EZ, a total contact casting system for diabetic foot ulcers, the *Medihoney* honey-based dressings for the management of wounds and burns, *Xtrasorb* for management of wound exudate, and *Bioguard* for protecting wounds against contaminants.

Derma also brings about 50 direct sales reps in the US, UK, and Canada, as well as global distributors. Derma has 300 people working in Princeton and has manufacturing operations in Memphis, Toronto and China. Its 2015 revenues were around $85m with mid-single digit annual growth and margins near 60%, Adruini said. Assuming the deal closes by the end of the first quarter of 2017 as planned, Derma will add about $65m to Integra's annual revenue in 2017 and be accretive to earnings by 2018. Integra's 2016 revenue was $992m.

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IBM Digs Deeper Roots In Medtech, As AdvaMed Builds Digital Footprint

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Over the past week **IBM Life Sciences** has made several big announcements that reflect a growing focus in the medtech space, including partnerships with **Illumina Inc.** and FDA. The company also recently became a member of AdvaMed's newly established Digital Health section, setting up the hallowed technology firm to play a more active role in lobbying in the medical device sector.

On Jan. 9, IBM and Illumina announced a partnership to use the *IBM Watson Health* machine learning tool to analyze and interpret genomic data from Illumina's *TruSight Tumor 170* solid tumor panel test. The panel is capable of detecting variations in 170 known genes.

According to Illumina, combining the test with Watson will allow providers to

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process tens of thousands of scientific articles and clinical trials to help interpret the variations on those genes within minutes.

"To enable precision cancer medicine on a large scale, we need new tools to overcome the data barriers of genomic research," said John Leite, vice president of oncology at Illumina. "With a comprehensive assay of Illumina and the power of Watson, we hope to deliver a rapid turnaround of the genomic alteration results."

Two days after Illumina and IBM announced the partnership news came that Watson was going to be used by FDA to explore sharing health data using "blockchain" technology. The technology is typically associated with the electronic currency bitcoin that is intended to provide more accountability and transparency during transactions.

FDA and IBM say applying blockchain technology to health data exchange can help address concerns with patient data security and breaches of patient privacy.

"The health care industry is undergoing significant changes due to the vast amounts of disparate data being generated. Blockchain technology provides a highly secure, decentralized framework for data sharing that will accelerate innovation throughout the industry," said Shahram Ebadollahi, vice president for Innovations and Chief Science Officer at IBM Watson Health in a company statement.

Initially, IBM and FDA plan to investigate blockchain technology in areas such as clinical trials and real-world evidence data gathering. They plan to evaluate the technology for two years and FDA plans to publish the initial findings sometime this year.

IBM has already been building up its footprint in the health-care space. Almost a year ago the company acquired Truven Health Analytics for $2.6bn to create what it called would be the "largest and most diverse" repository of health-related data. During a similar time frame, the company also announced it was buying two health database management start-ups and partnering with major players like **Johnson & Johnson, Medtronic PLC** and Apple, to allow them to use their Watson Health Cloud system to share medical.

ADVAMED'S NEW DIGITAL ARM

IBM's moves align with a growing focus by tech players in the medtech space. The trend is largely fueled by data analytics, which allows devices to input data and output useful information for patient care. The reason these efforts are accelerating now is linked to new wireless and mobile health products that have made it easier to gather data, but also because processing power allows analysis of large amounts of data more conveniently and faster.

> "We already have Google and Apple and IBM and Qualcomm and others, in our group, so we think we are capturing a critical mass," AdvaMedDx's Andrew Fish says.

Device trade group AdvaMed is looking to leverage trend by forming a new "sector" within the association. The group publicly launched AdvaMed Digital in December, and IBM joined the association in 2016, showing its commitment to becoming a major player in medtech.

Other members of the top tier of tech also become new members of AdvaMed in last year, including Apple, Google and Qualcomm, according to Andrew Fish, who is the executive director of AdvaMedDx.

Fish says AdvaMed's digital health arm is still very new but he expects it to expand very rapidly. "We already have Google and Apple and IBM and Qualcomm and others, in our group, so we think we are capturing a critical mass," he said Jan. 10 at the Medtech Showcase meeting in San Francisco, which was convened by the EBD Group, an Informa company.

Having the dedicated sector within AdvaMed will be a positive for future digital-health policy development, Wade Ackerman told Fish during a panel discussion. Ackerman was a senior health staffer for the Senate Health, Education, Labor and Pensions committee up until this summer and helped craft the 21st Century Cares Act, which included a section reworking FDA's authority over certain software tools.

Now a partner at the law firm Covington and Burling, Ackerman said that while on Capitol Hill, he noticed a clear lack of cohesion among stakeholders in the digital health space, which he now hopes will be bridged with the new venture.

"This space has so many varied players, the thought consensus was not as present," he said. "So making those policy decisions and briefing the senators about where the statute should land was more difficult in this space, so I was excited to see you [create the digital arm]."

Fish says AdvaMed created the digital sector because they realized many device companies were going in different directions when trying to implement new tools in the digital space. As part of the transition, the group changed its membership requirements to attract more firms that may not be traditional medical device companies but who play an important role in the digital medtech arena.

"Companies don't have to be bringing a final product to the marketplace through FDA device regulations to be a member of AdvaMed Digital," said Fish. "We are taking membership from any company who makes a product or an app or application of some type in digital health."

As examples, he said new AdvaMed members could be developers of sensors that could be used by medical devices to collect data but who themselves don't develop a final medical device for marketing.

"Across digital medtech, one of the problems is definitional. What is digital health? What is digital medtech? We are trying to define that," Fish said. :"What we have done is sort of thrown open the doors widely, because digital health is really about this expanding world of new ways to capture information, to aggregate it, to assess, and find actionable direction out of it."

Fish also says AdvaMed Digital is not only focused on policy advocacy, but is also looking at trends in the industry to figure out where technology converges and what business models are likely to be successful.

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Philips Shooting For Spine Surgery Top Spot With Augmented Reality Tech

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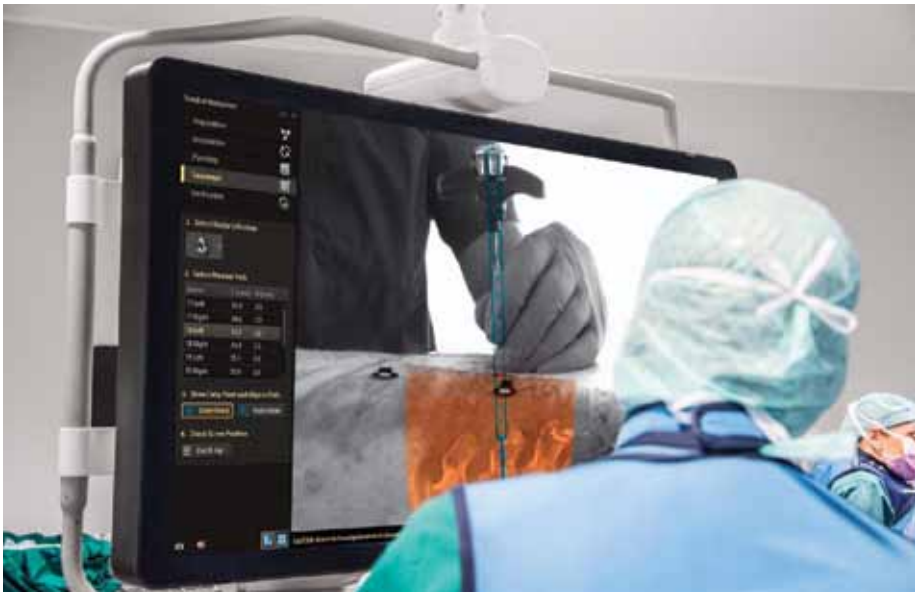
A new technology that will help spine surgeons better navigate the patient's anatomy during minimally invasive spine procedures could give Philips a leg-up in a market currently dominated by the likes of Medtronic and Stryker.

Philips' augmented reality (AR) surgical navigation technology works by using high-resolution optical cameras mounted on the flat panel X-ray detector to image the surface of the patient. It then combines this external view captured by the cameras with the internal 3D view of the patient acquired by the X-ray system to construct a 3D augmented-reality view of the patient's external and internal anatomy, in real-time. "The fact that the internal and external images are registered in real-time, so even if the patient shifts or the operating table moves, that is taken into account [in the augmented reality view] – this what's unique and patented in the technology," Ronald Tabaksblat, Business Leader of Philips' Image Guided Therapy Systems (IGTS) unit, told *Medtech Insight*.

By enhancing the surgeon's view of the patient's spine, this would enable more accurate implant placement, potentially in a shorter time, and ultimately improve patient outcomes.

The technology is still at an early stage of development and only been assessed in a preclinical study so far. However, results from this study – published in Spine last year – showed that the surgeons using the AR technology to help them place pedicle screws into the patient's spine during minimally invasive surgery were able to do so with a higher level of accuracy than without the aid of the technology (85% vs 64%, $p<0.05$). The firm worked with Sweden's Karolinska University Hospital and the Cincinnati Children's Hospital Medical Center in the US on this preclinical study and it is collaborating with other clinical centers to advance the clinical development of the technology. Tabaksblat said that the first-in-man study is expected to be carried out in "the coming weeks".



Source: www.philips.com

Philips' 3D Augmented Reality Surgical Navigation Technology For Minimally Invasive Spinal Surgery

A large part of Philips' IGTS business has mainly been in coronary and vascular interventions, following its $1bn acquisition of Volcano, the intravascular ultrasound imaging specialist, two years ago. This had set Philips apart from other large surgical navigation players like Medtronic, BrainLab and Stryker. "This AR solution is completely new and really sets us up to be a big player in spine surgery, which we haven't been before," said Tabaksblat, adding that it would also move Philips more closely into fields where the likes of Medtronic are active.

The AR technology is currently designed for use in hybrid operating rooms, which incorporate advanced medical imaging devices to enable surgical and minimally-invasive endovascular procedures to be performed. Philips has over 750 hybrid ORs installed globally; Tabaksblat said that the current version of the AR technology is designed for use in hybrid ORs but there is the possibility for it to evolve so that it could be used in general surgical settings, "but that is in the future."

The company declined to specify a timeline for when it expects the technology – which would take the standard CE marking and US 510(k)-clearance regulatory routes for approval – to be commercially available. While its efforts are focused very much on spine surgery for now, it is also exploring the use of the AR technology in cranial and trauma surgery.

Spine surgery was traditionally an "open surgery" procedure, accessing the affected area via a large incision so that surgeons could physically see and touch the patient's spine in order to position implants such as pedicle screws. In recent years, however, there has been a shift towards minimally-invasive techniques, performed by manipulating surgical tools through small incisions in the patient's skin in order to minimize blood loss and soft tissue damage, and consequently reduce postoperative pain. However, getting a clear view of the patient's anatomy is a constant challenge for surgeons performing minimally invasive surgery, and the use of surgical navigation systems are designed to address this challenge.

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Irish Authority Takes Action To Avoid IVD Regulation Bottlenecks

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The Irish agency responsible for medtech products says it is actively seeking "expressions of interest" from national laboratories to be designated as EU reference laboratories in the context of the future IVD Regulation. Laboratories have until Jan. 31, 2017, to submit their expressions of interest, according to the notice from the country's Health Products Regulatory Agency (HPRA).

It seems that Ireland is the first of the EU authorities to have made a public call for greater capacity to assess IVD files for higher-risk products. More resources will necessary to establish essential services for the higher-risk IVDs under the forthcoming IVD Regulation, which is still yet to be adopted in its final form by EU authorities. Other EU member-state authorities are likely to follow suit.

HPRA notes that the proposed IVD Regulation is expected to be adopted in the first quarter of 2017. If so, it will take effect before the end of the first half of 2017. Others suggest the regulation might not be adopted until the second quarter.

The requirements concerning reference laboratories, however, will only apply from six months prior to the full application of the IVD Regulation, according to the current IVDR text. Because a five-year transition period is anticipated for the IVD requirements, the reference laboratory provisions will not apply until, likely, the end of 2021.

But if reference laboratories are not appointed until that time, it will likely lead to a bottleneck as manufacturers all apply at the same time to use the services of the laboratories. The risk is that some companies will fail to meet the IVDR requirements in time. (See box, "Failure To Comply On Time?")

Under the IVD Regulation, reference laboratories will be involved in performance and compliance testing in both the pre-market and post-market phase for the higher-risk IVDs – those in class C, such as cancer diagnostics, and class D, which are IVDs intended to detect a transmissible agent in blood or cells to assess suitability for transfusion.

HOW MANY REFERENCE LABORATORIES WILL BE NEEDED?

Based on how reference laboratories work in other sectors, it seems likely that there will be reference laboratories dotted around Europe that are granted financial aid from the European Commission to perform work in support of the sector. No one knows quite how many laboratories will be needed, but it could be as many as 30, one medtech expert suggested to *Medtech Insight*.

CLICK

For a full list of IVD classifications, see the classification rules in the latest version of the proposed IVD Regulation text, in Annex VII of the document made available in June 2016.

Some of the EU reference laboratories within the commission's Joint Research Centre are likely to be candidates under the IVD Regulation.

ROLE AND TASKS

The role of the reference laboratories will include providing scientific and technical assistance to the EU Commission, member states and notified bodies. The laboratories will also assess compliance of class D high-risk IVDs with applicable Common Specifications. (Common Specifications are more detailed than standards, and while not mandatory, any company not complying with them would have a very difficult time explaining the gap in the case of a safety incident and subsequent legal challenge.)

The Irish authority spells out the tasks of the reference laboratories for class D (highest risk) as follows:

- Carry out appropriate tests on samples of manufactured class C devices or batches of class D devices;
- Provide scientific and technical assistance to the commission, the Medical Device Coordination Group (MDCG),

Failure To Comply On Time?

A growing number of EU stakeholders are worried that many IVD companies will not have time to prepare for compliance against the forthcoming IVD Regulation. Despite a five-year transition period, the new regulations introduce many changes that will be difficult for the sector to manage with its current resources.

At the center of this problem is the fact that there will be a shift from notified bodies being involved in about 15% of IVD products under current EU directors to notified bodies having to assess 85% of IVDs or event more under the future regulations. There are not enough notified bodies active in this sector at present to address the oncoming demand.

Not only will manufacturers need to gear up, but they will need to find notified bodies with capacity to audit their products. Notified bodies will not just be challenged by the IVD industry, but their resources will also likely be tied up managing the huge flood of medical devices manufacturers that are seeking compliance before the likely mid-2020 deadline for the new EU Medical Devices Regulation. Overall, the potential for severe delays in mandatory IVD audits and risks to continued availability of IVDs on the market are real.

the member states and notified bodies in relation to the implementation of the regulation;
- Provide scientific advice regarding the state of the art in relation to specific devices, or a category or group of devices;
- Contribute to the development of CS and of international standards; and
- Provide scientific opinions in response to consultations by notified bodies in accordance with the IVD Regulation and publish them by electronic means after consideration of national provisions on confidentiality.

At the request of a member state, the commission may also designate EU reference laboratories where a member state wishes to have recourse to such a laboratory to ensure the verification of the claimed performance and the compliance of class C devices with the applicable Common Specifications when available, or with other solutions chosen by the manufacturer to ensure a level of safety and performance that is at least equivalent.

FINANCING AND OVERSIGHT

HPRA says that when it comes to financing, EU reference laboratories may get a financial contribution from the EU.

It adds that the commission will specify, through implementing acts, the structure and level of fees that may be applied for notified bodies or member states requesting scientific or technical assistance or a scientific opinion from an EU reference laboratory.

EU reference laboratories will be subject to controls, including on-site visits and audits by the commission to verify compliance with the requirements of the regulation.

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MDR GUIDANCE:

Most User Errors Should Be Tracked, Not Reported As Adverse Events, FDA Says

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Manufacturers whose devices malfunctioned simply because they were used incorrectly don't have to file adverse event reports with FDA. Rather, firms should track and trend that quality information and escalate reports of user error when necessary.

The US agency makes that clear in Sec. 2.6 of its guidance, "Medical Device Reporting for Manufacturers." Released in November, the document also includes a bevy of other advice, including MDR reporting requirements around contract manufacturing, exemptions and product problems discovered in literature, and serves as a general roadmap for how firms should structure MDR programs.

"If you determine that an event is solely the result of user error with no other performance issue, and there has been no device-related death or serious injury, you are not required to submit an MDR report, but you should retain the supporting information in your complaint files," the guidance states.

That instruction was included in the final version of the guidance but not in the 2013 draft document. The language was added, attorney Jennifer Newberger says, because industry needed FDA to make clear that companies don't have to file a flurry of MDRs each time a fault-free product is wrongly used.

Many manufacturers "have questions about user error, about when to report," said Newberger of the law firm Hyman, Phelps & McNamara. "It's often a struggle because people do not always use products properly, and there's always a question of how much responsibility a company really does have to report. So, I'm glad that FDA included that sentence" in the final MDR guidance.

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"There probably could have been a little bit of explanation around it, but I think it will be very helpful knowing that a single event of user error does not need to go through an entire MDR evaluation," she added. "But certainly companies should still track this information because repeats of user error could indicate an actual problem."

There was no mention of user error in a 1997 FDA guidance on Medical Device Reporting, which industry had been using for adverse event advice before the new document was released in November. That's another reason why some instruction around

user error and adverse event reports was needed, Newberger said – because some firms fail to report MDRs related to user error at all, even when it's warranted.

"I've seen a number of companies that have language in their procedures that actually say, 'We don't need to report user error,' and I always reply to them, 'Yes, you do.' User error is within the [Medical Device Reporting regulation, 21 CFR, Part 803], because malfunctions can indeed be due to user error," Newberger told *Medtech Insight*.

FDA backs that up in its final guidance. User errors "often reflect problems with device labeling, the user interface, or other aspects of device design," the document states. "Thus, FDA believes that these events should be reported in the same way as other adverse events, which are caused or contributed to by the device."

> "I've seen a number of companies that have language in their procedures that actually say, 'We don't need to report user error,' and I always reply to them, 'Yes, you do,'" attorney Jennifer Newberger says.

CONTRACT MANUFACTURING: WHEN EXEMPTIONS ARE NEEDED

Meanwhile, the guidance notes in Sec. 2.17 that contract manufacturers don't have to file Medical Device Reports if they don't distribute or market the products they're making. Instead, those reporting duties would fall squarely on specifications developers' shoulders.

And the document makes clear that those types of contract manufacturers don't have to file an exemption request with FDA to avoid MDR reporting. Such language was absent from the 2013 draft.

"If you're a contract manufacturer, and you manufacture the product for a spec developer and you deliver it back to the spec developer, and it's the one distributing and marketing, then under the clarification in the final guidance, the contract manufacturer won't be subject to MDR reporting in the first place. So, you don't have to seek an exemption," Michele Buenafe, a partner with the law firm Morgan Lewis, said in an interview.

But for all other contract manufacturers that do distribute and market, they will be obligated to report, along with their spec developers. To avoid unnecessary duplicative reporting, FDA says contract manufacturers and spec developers can come together to determine which of the two will oversee MDR reporting duties. The firms would then file a joint exemption request with the agency.

Such direction was not found in the 1997 MDR guidance. Before now, FDA left it up to the two firms to decide how best to report and didn't require exemption requests.

"Even before this exemption request requirement hit the draft guidance in 2013, we had been getting feedback from FDA that that's what they wanted. And so there was some awareness in industry, through enforcement or through communications during facility inspections, that FDA had shifted its position and that it expected either contract manufacturers or spec developers to ask for an exemption," Buenafe said.

The guidance also points out that exemption requests can be pulled by the agency. "If Firm A is designated to submit the MDR reports, but failed to do so, we would consider such a failure to report to be sufficient grounds to revoke Firm B's exemption from reporting," it states. "If revoked, both Firms A and B would be required to report MDR-reportable events in compliance with all applicable MDR regulations."

And, for example, "if the contract manufacturer – who isn't the reporter – is getting complaints and it's not sharing those complaints with the spec developer – who is the reporter – then that's going to be a problem, and FDA makes that clear in its language in the guidance," Buenafe told *Medtech Insight*. "So, you can get an exemption for this, but keep in mind that you're still going to be on the hook if something goes wrong."

ALARMS LANGUAGE REMOVED

The final guidance removed language found in the 2013 draft that concerned manufacturers of devices that include alarms.

The draft stated: "If the device malfunctions but an alarm alerts the user to intervene before there is any harm to the patient, the

Guidance Gives FDA Enforcement Leverage

When FDA goes after manufacturers for not reporting, it's usually because there is a disconnect between what they think they have to do and what they actually have to do, Wiley Rein attorney Sonali Gunawardhana said in an interview with *Medtech Insight*. That's why the MDR guidance was needed.

"This guidance document is pretty good in the respect that you have the agency being far more transparent in saying, 'Hey, this is what we expect from you.' It is best practices as you move forward," said Gunawardhana, a former FDA device center regulatory counsel.

"And I think it's all based on questions FDA has received over the years," she said. "FDA hears manufacturers repeatedly say, 'What am I supposed to do again?' So, the agency said, 'OK, these people don't necessarily understand this stuff, so let's just put it out there.' And the reality is, if you put it out there, firms can't come back and say they don't understand. It puts FDA in a stronger place in terms of enforcement."

event should be reported as a malfunction because of the potential to cause or contribute to a death or serious injury if the malfunction recurred, and either the alarm did not work or there was no one to respond."

This led manufacturers to believe that an adverse event report would have to be filed each time a device's alarm was triggered.

"But in the final guidance [in Sec. 4.13.1], the issue of how to address alarms was removed altogether," attorney Newberger said. "The fear was that if an alarm is to be reported as an MDR, then companies are going to be reporting every time a machine alarms, which is clearly not a malfunction."

She says the removal of the alarms language in the final guidance "sort of leads back to the companies to, I suppose, take each situation on a case-by-case basis and figure out how they think alarming should be addressed," she said. When it comes to alarms, "it's an important issue, but it remains unaddressed."

"You can get an exemption ... but keep in mind that you're still going to be on the hook if something goes wrong," attorney Michele Buenafe says.

WILL FDA'S 'TWO-YEAR' NOTICES REQUEST BE IGNORED?

Manufacturers under Sec. 2.15 of the guidance can continue using a "two-year rule" that lets them stop sending MDRs to FDA if there are no additional product problems after 24 months. That rule was found in the 1997 MDR guidance but was left out of the 2013 draft.

The draft instructed firms to seek exemptions from the agency to stop reporting, raising the ire of some in industry who said FDA would be inundated with exemption requests and that the requests would overly burden manufacturers.

After a product fails, there is a presumption that the problem will occur again "until either the malfunction has caused or contributed to no further deaths or serious injuries for two years, or the manufacturer can show through valid data that the likelihood of another death or serious injury as a result of the malfunction is remote," the final guidance reads.

At the end of two years, FDA recommends that manufacturers submit a notification to the agency with a "summary of the data and the rationale for your decision to cease reporting."

"Yes, the final guidance brings back that two-year rule, but it still says that FDA recommends you submit a notification to FDA with a summary of the data and rationale for your decision to cease reporting at the end of two years," attorney Buenafe said.

"So, they're still recommending an additional step – that you at least notify FDA that you're stopping reporting. But I don't expect a lot of those notices to go to the agency, really," she said.

Rather, it might just serve as a discussion point during an FDA facility inspection, Buenafe surmises. "If that happens, then the FDA investigator will probably expect you to have a rationale behind ceasing reporting at the end of two years. So, it might be something that gets looked at in an inspection, but it's highly unlikely that firms are going to start submitting those notices to FDA."

The guidance points out that firms "can request an exemption … from further reporting sooner than two years if your analysis of the data supports your conclusion that the malfunction has not caused or contributed to further deaths or serious injuries, and that the likelihood" of deaths and injuries happening is determined to be remote.

"FDA does say that if you want an exemption sooner, then to simply request one," Buenafe said. "But I think that's unlikely to happen too."

LOOK TO THE LITERATURE

Manufacturers should investigate adverse events it learns about in literature, the guidance states. In fact, the agency suggests that firms go one step further and get in touch with article authors.

"You must investigate each event reported in [a] literature source to determine if the information represents an MDR-reportable event," the guidance states in Sec. 4.16.2. "If the information in the literature source and/or your investigation of the cited events reveals specific information about all or some of the reportable events, then you will need to report these events as individual reports."

It goes on: "For example, you could contact the author of the literature source and request information about all or some of the patient and/or device-related events."

"If an article suggests adverse events, and there is just not enough information in the article to determine whether it's reportable, or if there's some critical piece of information that is needed, FDA may expect you to at least attempt to contact the author," Buenafe said.

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Zimmer Biomet To Settle Overseas Bribery Charges With US DOJ

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Zimmer Biomet Holdings Inc. will pay $30.5m to settle allegations that the company's actions in Mexico and Brazil violated the Foreign Corrupt Practices Act (FCPA), the US Department of Justice announced Jan. 12.

The payments stem from allegations that **Biomet Inc.** paid bribes to Mexican government officials and violated the FCPA's internal controls provision in Mexico and Brazil. In addition, the company's actions breached a 2012 deferred prosecution agreement between the Department of Justice and Biomet. The agreement had been set to expire in 2015, but DOJ extended it based on allegations of ongoing misconduct.

The company's behavior forced DOJ to move ahead with criminal charges, said Leslie Caldwell, assistant attorney general of the Justice Department's Criminal Division.

"Zimmer Biomet had the opportunity to avoid criminal charges, but its misconduct allowed the bribes to continue," she said. "…In appropriate circumstances the department will resolve serious criminal conduct through alternative means, but there will be consequences for those companies that refuse to take these agreements seriously."

DOJ says that Biomet kept using a Brazilian distributor that was known to have bribed government officials on Biomet's behalf, even after the deferred prosecution agreement. Biomet also didn't put adequate internal accounting controls into place at its Mexican subsidiary, Biomet 3i Mexico S.A. de C.V., even though the government warned that the subsidiary appeared to be paying bribes. The subsidiary was bribing customs brokers and sub-agents so they would let Biomet 3i import contraband dental implants that lacked proper registration or labeling, which violated Mexican law.

In addition to a $17.4m criminal penalty, Zimmer Biomet signed a new deferred prosecution agreement that requires it to maintain an independent corporate compliance monitor for three years. Meanwhile, subsidiary JERDS Luxembourg Holding S.ár.l. agreed to plead guilty on a charge its actions caused Biomet and Biomet 3i to violate the books and records provision of the FCPA.

Zimmer Biomet is also set to pay $13m to the Securities and Exchange Commission to resolve a cease and desist order. The settlement includes a disgorgement of $6.5m and a civil penalty of $6.5m.

In a statement, Zimmer Biomet said it was "pleased" to reach the resolution but noted that all the violations occurred before Zimmer's 2015 purchase of Biomet.

The payments won't affect Zimmer Biomet's financial outlook, the company said.

The Zimmer settlement was one of two health-care-product-related settlements announced by DOJ on Jan. 12. In the second, **Baxter Healthcare Corp.** agreed to pay more than $18m to resolve allegations the company violated good manufacturing practices in its North Carolina IV drug manufacturing operations.

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Hospitals Prefer Existing Mechanisms To Report Device Safety Issues, Says AHA

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Both hospitals and manufacturers seem reluctant to change the status quo on reporting adverse events involving devices at user facilities such as hospitals, according to comments and testimony provided in response to a Dec. 5 US FDA workshop on the role of hospitals in modernizing evidence generation for device evaluation.

"The AHA recommends that FDA examine existing safety efforts, and particularly the role of patient safety organizations, to determine the extent to which the agency can leverage current reporting streams to gather evidence about medical device safety, rather than relying on a separate and potentially duplicative reporting structure," wrote the American Hospital Association's Ashley Thompson in Jan. 6 comments.

MedSun was hailed by FDA and hospitals for doing a good job in capturing adverse events information at hospitals, but its scope was seen as somewhat limited.

Currently, FDA relies on a network of 300 hospitals, known as the Medical Product Safety Network, or MedSun, to track device use, errors and events in a real-world environment, said FDA device center chief Jeff Shuren in a Nov. 8 agency blog post.

But such reporting does not also supply a complete picture, and in October, a series of high-profile safety alerts at hospitals prompted FDA to inspect facilities for their compliance with adverse-event reporting regulations, an exercise revealing FDA-483 form violations at 15 of 17 hospitals the agency inspected.

In the future, FDA hopes the hospital community can effectively work with the hospital community so they will participate in a joint effort by FDA and manufacturers – the National Evaluation System for health Technology, or "NEST" – by using software tools and electronic health records to help capture more reportable device adverse events.

The purpose would be to help FDA and manufacturers in post-market surveillance efforts, so they know what modifications to make to devices, to be sure they are safer, or used more safely, in the future.

AHA acknowledged that user facilities such as hospitals must report any medical device-related deaths or serious injuries to the agency within 10 workdays, and said it is "confident that hospitals will be able to participate effectively in NEST once more active software tools – such as advanced electronic health records, are put into place at facilities."

The group also commented it supports use of electronic reporting using online forms, such as those used by MedSun hospitals, to make reporting of adverse events less burdensome and more efficient.

MITA SAYS FDA SHOULD REQUIRE EQUIPMENT SERVICES TO REPORT EVENTS

At a Dec. 5 workshop in Silver Spring, Md., to gather more comment on how to involve hospitals to modernizing their data collection efforts to improve evidence generation, Peter Weems, director of policy & strategy for the Medical Imaging & Technology Alliance, cited an important gap in reporting from companies that service large pieces of hospital equipment, including imaging equipment.

"Really, there is not a good understanding of service-related events," Weems remarked. "Not everybody who services a medical device is held to the same quality, safety and reporting requirements" as are manufacturers, he added.

Weems pointed out that if service companies were required to report adverse events they see with equipment, it would provide "a great deal of information" to other initiatives the agency is working on, such as Unique Device Identifiers. In addition, "this data is very valuable to original equipment manufacturers," he added, which are the primary party on the hook for capturing, analyzing and reacting to adverse events.

> Electronic health record software needed to collect adverse event reports many not be ready yet for post-market surveillance of medical devices, physician Jay Ronquillo says.

"Therefore, it is the position of MITA that these parties who service equipment should be required by FDA to report these problems also," he told agency staff at the workshop.

Also at the Dec. 5 meeting, an industry VP told FDA that malfunctions that hospitals and equipment services see with devices can be considered "reportable," and should be relayed to FDA. "Many of the adverse events being described today are actually malfunctions, and user facilities should be telling FDA about them," said Elisabeth George, VP of global government affairs for **Philips Healthcare**.

But while hospitals could be playing a key role in evidence generation and adverse-event reporting for NEST, the electronic health record software needed to collect such reports many not be ready yet for post-market surveillance of medical devices, testified Jay Ronquillo, a physician at Massachusetts General Hospital and biomedical engineer who spoke on behalf of the National Center for Health Research, a patient-safety focused group.

DEVICE SOFTWARE AND REPORTING

And when it comes to software found in devices, there are challenges there, too, Ronquillo says.

"Software is a critical component of many medical devices, from implantable cardiac pacemakers to drug infusion pumps, to health IT-like electronic health records and clinical decision support. However, software-related errors for medical devices are complex," he said in his Dec. 5 testimony.

Software errors can be hard to identify and clearly separate from other types of problems, such as human error or mechanical failure, the physician maintained.

He added, "Software vulnerabilities also represent a growing cybersecurity concern that could directly affect individual patients, and even populations. As a result, accurate risk assessment and adverse event reporting will require clear guidance regarding how all types of software malfunctions are measured, monitored and could impact patient care. We currently do not have that guidance today," Ronquillo stated.

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ACA Repeal With Device Tax Demise Due Next Month

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Senate Republicans began the process of eliminating the Affordable Care Act, passing a key budget resolution bill, S.Con.Res. 3, on Jan. 12, paving the way for further action on a repeal and replacement package that will include device tax repeal, House Ways and Means Chair Kevin Brady, R-Texas, said.

"A repeal bill is slated to be on the president's desk in February … it is his hope we have it to him in that month, that's the timetable we will be working on," Brady told radio talk show host Hugh Hewitt on *The Hugh Hewitt Show* on Jan. 11. Brady also confirmed that the medical device tax would be part of a final ACA repeal bill.

Medtech industry leaders are primarily focused on removing the 2.3% device excise tax that was enacted by the ACA, and AdvaMed reaffirmed this goal Jan. 12. The trade group encouraged the Senate to permanently repeal the tax, as laid out in legislation reintroduced by Sens. Orrin Hatch, R-Iowa, and Amy Klobuchar, D-Minn. A similar measure was reintroduced in the House by Rep. Erik Paulsen, D.-Minn., the first week in January.

"Senate introduction of this legislation brings us one step closer to eliminating the burdensome tax, which has proven to be a drag on the medical technology industry's ability to innovate on behalf of their patients," said Scott Whitaker, AdvaMed president and CEO.

BUDGET BLUEPRINT PACKAGE SETS STAGE FOR REPEAL

The budget resolution package was agreed to by Republicans Jan. 12, by a 51 to 48 party-line vote. The budget blueprint bill gives House and Senate committees until Jan. 27 to introduce ACA repeal legislation, and the House was poised to vote on it on Jan. 13.

During debate on the budget package, Democrats offered a series of amendments to preserve some of the important elements of ACA, including guaranteed coverage and no lifetime limits for people with preexisting conditions, for maternity care, to bolster children's' health-care coverage, and for mental health care, but they were all voted down.

A key Senate committee chairman, Sen. Lamar Alexander, D-Tenn., described Senate leaders' plan for what they believe will be a smooth transition for individuals from coverage under ACA to coverage under a new Republican plan. Alexander is chairman of the Senate Health, Education, Labor and Pensions Committee, which will have a major hand in shaping any Republican replacement plan for ACA.

"While we build a replacement, we want the 11 million Americans who now buy on the exchanges to be able to continue to buy private insurance," Alexander said. He noted that Congress and the president would have to take action before March 1 because this is when insurance companies begin to decide if they will offer insurance in markets during 2018.

The goal of those putting together the Republican health-care replacement plan "is to allow any state-approved plan to count as health insurance under the Obamacare rules."

Other ideas, Alexander said, would be to allow individuals to use their existing ACA subsidies to purchase state-approved insurance outside Obamacare exchanges, and "permit states more flexibility to determine so-called essential health benefits."

HHS Secretary Sylvia Burwell warned in a recent speech that some of the ideas espoused by Alexander and other would provide insufficient coverage, most likely result in the loss of some benefits, including maternity care, prescription drug coverage and mental health care, and prevent many poor people from being able to afford to buy health coverage.

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Shire To Pay Record-Setting Device FCA Settlement

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Shire PLC and its subsidiaries will pay $350m to settle state and federal allegations the manufacturer paid kickbacks and used other illegal means to encourage providers to use its *Dermagraft* human skin substitute. The product was FDA-approved to treat diabetic foot ulcers.

This is the largest civil settlement to date in a device-related False Claims Act case, the Department of Justice said in announcing the Jan. 11 agreement.

Shire purchased Dermagraft creators Advanced BioHealing in 2011. It sold the product to **Organogenesis Inc.** in 2014.

Dermagraft salespeople enticed clinics and physicians to buy the product through several means, including "lavish dinners, drinks, entertainment and travel; medical equipment and supplies; unwarranted payments for purported speaking engagements and bogus case studies; and cash, credits and rebates," DOJ said in a statement. The company also reportedly violated anti-bribery law by offering kickbacks to physicians employed by the US Department of Veterans Affairs (VA).

The $350m also settles allegations that Shire and its predecessor, ABH, illegally

marketed Dermagraft for off-label uses; made false statements to inflate the price of Dermagraft; and caused improper coding, verification or certification of Dermagraft claims.

In total, the Dermagraft violations lead providers to illegally bill federal healthcare programs for hundreds of millions of dollars, DOJ says.

The allegations arose via six whistleblower lawsuits, all of which were filed in the Middle District of Florida.

Several law enforcement agencies participated in the investigation, including the DOJ Civil Division's Commercial Litigation Branch; the US Attorneys' Offices for the Middle District of Florida, District of Columbia, Middle District of Tennessee and Eastern District of Pennsylvania; the FBI; the US Department of Health and Human Services Office of Inspector General; the VA OIG and the Department of Defense Criminal Investigative Service.

Shire, which cooperated with the investigation, has been operating under an HHS Corporate Integrity Agreement since 2014 as part of a separate $56.5m False Claims Act settlement involving the company's marketing of four drugs to treat ADHD and ulcerative colitis.

"We are pleased to have reached a resolution on this matter, and believe that the terms of the resolution reflect Shire's extraordinary cooperation with the Department of Justice throughout its lengthy investigation," said Shire spokeswoman Debbi Ford.

This is not the only particularly expensive DoJ device case to come to completion recently. Last March, Olympus Corp. was hit with a $632.2m penalty, including criminal and civil payments, which DoJ was the largest total amount paid in US history for violations involving the Anti-Kickback Statute by a medical device company.

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Stay Of Execution In EU For Environmental Shortfall Devices

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The European Commission is expected to propose an amendment to the Directive on the Restriction of Hazardous Substances (RoHS2) so that the supply and the resale of non-RoHS compliance electronic medical devices, IVDs and control instruments may continue beyond July 22, 2019.

If this happens it this means that these electronic devices may be further supplied in the distribution chain or resold after July 22, 2019 even if the deadlines for the ban on import and first marketing have passed, according to Candido Marcia Molyneux, Spanish counsel in the Brussels office of Covington & Burling. He wrote about the matter in the National Law Review.

This imposition of the 2019 deadline, he says, would severely restrict the continued supply of new devices that are still in the supply chain, as well as the resale and second-hand market of used, repaired or refurbished devices.

The following ban dates have, or are, being applied for first import or marketing in the EU and European Economic Area:

- **July 22, 2014:** Import and first marketing of non-compliant electronic medical devices and electronic monitoring and control instruments;
- **July 22, 2016:** Electronic IVDs; and
- **July 22, 2017:** Electronic industrial monitoring and control instruments.

The EU Commission's anticipated proposal is also likely to seek an exemption for non-compliant spare parts and cables for the repair and reuse of products that are newly covered by the first import or marketing bans. Such products might include devices used to analyze DNA material, or the interface equipment between a patient's computer and its self-testing IVD medical device.

It is likely to take at least 18 months before the proposal reaches the stage where it is adopted at EU level.

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