POLICY & REGULATION
US FDA's take on applying real-world data, p. 14

COMMERCIAL
Inhalation device market snapshot, p. 10

R&D
ESC flutters with afib data, p. 5

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5 FIGURES ON 510(K) EXEMPTIONS:

What's The Impact Of US FDA's Recent Actions?

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The US FDA's recent congressionally directed actions to exempt reams of devices from 510(k) requirements may have less of an impact on industry and agency workloads than the top-line numbers suggest, according to an analysis performed by *Medtech Insight* in collaboration with regulatory intelligence firm Graematter Inc. But there are pockets of companies and clinical specialties where the effects might be more pronounced, the analysis found.

In July, FDA issued a Federal Register notice listing several hundred class II devices that it was exempting from 510(k) requirements. *(Also see "US FDA: 510(k)-Exempt Class II Devices Should Withdraw Applications" - Medtech Insight, 11 Jul, 2017.)* That followed an April notice exempting 72 class I devices from pre-market submissions. *(Also see "FDA 510(k)-Exempts 72 Devices, Mostly Diagnostics" - Medtech Insight, 12 Apr, 2017.)*

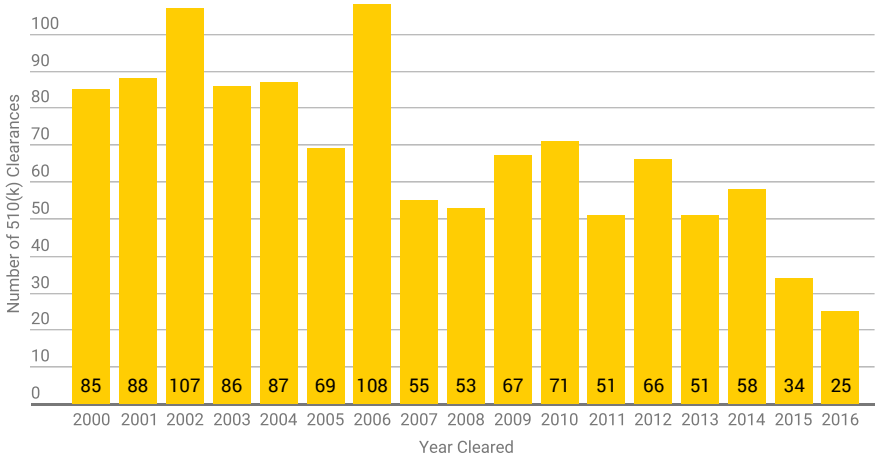
The actions were required by a provision in the December-enacted 21st Century Cures Act intended to "decrease regulatory burdens on the medical device industry" and "eliminate private costs and expenditures required to comply with certain federal regulations," FDA stated in its July 11 class II exemptions notice.

Medtech Insight worked with Graematter, applying its regulatory intelligence system to assess, in practice, how much burden might be reduced as a result of the Cures Act provisions and FDA notices. Graematter collects regulatory information from multiple sources, integrating the data into a single system. Consolidating the information into a single proprietary database allows visibility into the interconnections and trends hidden within the data.

Our findings: A small subset of companies will see a tangible impact in terms of regulatory efforts and costs from the exemptions, but most firms will experience relatively small or no impact from the Cures-directed changes. Similarly, the exemptions will have a trivial effect on overall FDA staff workload, but it could

FIGURE 1

510(k)s Cleared For Newly Exempted Codes, 2000-2016



Source: Graematter Inc.

CONTINUED ON PAGE 12

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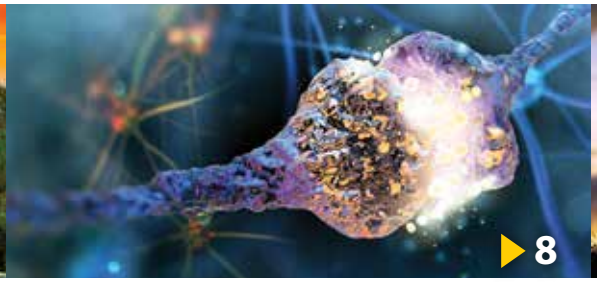

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On the latest podcast, we discuss market intelligence features on point-of-care testing and ocular drug delivery. Next, look for a discussion on recent FDA policy analyses in *Medtech Insight*'s weekly podcasts where journalists discuss topics impacting the device and diagnostics sector.

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inside:

Medtech insight

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POLICY & REGULATION

ESC 2017: News Flutter With AFib Data

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Results from the CASTLE AF study showing that catheter ablation improves outcomes for patients with left ventricular dysfunction and atrial fibrillation (AF) headlined results reported from AF trials at the European Society of Cardiology congress in Barcelona Aug 26-30.

Nassir Marrouche of the University of Utah in Salt Lake City presented the results from the **Biotronik**-sponsored trial during a Late-Breaking Clinical Trials session August 27. *(Also see "ESC 2017: CASTLE AF, REVEAL AF Among Noteworthy Device Trials To Be Presented in Barcelona" - Medtech Insight, 24 Aug, 2017.)* "AFib and heart failure are very intertwined and married together," Marrouche said in a webcast from the ESC meeting. About 30% of heart failure patients have AFib and these patients have a worse prognosis than heart failure patients without AF. "AFib still presents a major dilemma. Even the guidelines lack a straightforward suggestion or recommendation on how to treat these patients, so we have a variety of options, because there's no single study that shows one treatment is better than the other."

CASTLE AF randomized 397 patients with symptomatic paroxysmal or persistent AF and heart failure with a left-ventricular ejection fraction of less than 35% to radiofrequency catheter ablation or conventional medical therapy. All patients were implanted with a Biotronik implantable cardioverter defibrillator linked to the *Home Monitoring* network for continuous surveillance of AF. The ablation method was left up to the individual operators, but pulmonary vein isolation ablation was used in 98% of the patients.

During the median follow-up of 37.8 months, the primary endpoint – a composite of all-cause mortality and unplanned hospitalization for worsening heart failure – occurred at a significantly lower rate in the ablation group (28.5%) versus the control group (44.6%). The secondary endpoints of all-cause mortality (13.4% vs 25%) and heart-failure hospitalization (20.7% and 35.9%), measured separately, were also significantly lower in the ablation group than in the conventional treatment group. Overall, patients treated with ablation were 47% less likely to die, and 44% less likely to be hospitalized with worsening heart failure than patients treated with conventional therapy.

Commenting on the CASTLE-AF results at the congress, Carina Blomstrom-Lundqvist of Uppsala University in Sweden also pointed out that the trial showed that nearly 70% patients treated with ablation maintained sinus rhythm at least five years after the procedure, "which is not the pattern you usually see," she said.

Marrouche pointed out that the trial is the first randomized study of AF ablation to show a difference in universally accepted "hard endpoints" like death and heart-failure hospitalization, rather than quality of life measures or AF-burden, which are not always defined the same way. This was a major strength of the study and also why it took almost nine years to complete the trial, he said.

The ICDs implanted in every patient may have affected mortality in both groups, Marrouche said. And Blomstrom-Lundqvist pointed out that every patient's heart failure treatment was optimized before they were randomized, so "there could be some bias here – that you would optimize patients better with ablation better than those receiving antiarrhythmic drugs."

Marrouche's recommendation to electrophysiologists treating heart failure patients with AF is to "ablate them early on, very soon in the disease stage."

Marrouche's recommendation to electrophysiologists treating heart failure patients with AF is to "ablate them early on, very soon in the disease stage, before they get to a left-ventricular ejection fraction under 25% or New York Heart Association Class IV or advanced III." Blomstrom-Lundqvist agreed that "this is new information and I think we'll have to change our policy and be more deliberate and refer patients with atrial fibrillation and heart failure to catheter ablation." But, she cautioned, the trial only enrolled patients with symptomatic AF so the best approach for asymptomatic patients is still unclear.

CAPTAF SHOWS ABLATION IMPROVES QUALITY OF LIFE

Atrial fibrillation improved quality of life better than antiarrhythmic drugs could on their own in 155 patients with symptomatic AF in the CAPTAF trial, but both therapies produced similar reductions in AF-burden.

Carina Blomstrom-Lundqvist of Uppsala University in Sweden presented the one-year results from the trial at the ESC conference on August 29. CAPTAF was sponsored by the Swedish Research Council, Swedish Heart-Lung Foundation, and **Medtronic PLC** .

"The primary endpoint [in previous AF trials] has been 30-second AF recurrence on Holter monitors. But we would like to use, as the primary endpoint, quality-of-life, because that is the [goal] for AF procedures, and that has not been done before," she said in a webcast from the meeting. "We also thought that rhythm-monitoring to assess AF burden was important and that has not been done before."

CAPTAF randomized 155 patients with symptomatic AF who had already failed to respond to one rate or rhythm control drug and had at least one symptomatic paroxysmal AF episode in the previous two months, or at least two symptomatic episodes of persistent AF in the previous year. All patients were implanted with a cardiac monitor. Following a two-month run-in, they were randomized to ablation with pulmonary vein isolation or antiarrhythmic drug therapy with adequate dosages as specified in the professional guidelines.

After one year the ablation group showed a greater improvement in average overall health, as measured by a standard survey, than the drug group –11.0 points versus 3.1 points. In addition, all quality-of-life subscales, except for bodily pain and social functioning, improved significantly more in the ablation group than in the drug group. European Heart Rhythm Association Symptom Classification also improved significantly in the ablation group than in the drug group

The reduction in AF burden, defined as the proportion of time the patient spent in in AF, was larger in the ablation than in the drug group, but the difference was not statistical significant. The complication rates in both groups were similar.

"We have confirmed that quality-of-life is really improved [with ablation] and I think it's related to the side-effects of the antiarrhythmic drugs, although that has not yet been shown in this trial," Blomstrom-Lundqvist said.

PATIENTS FIND THEIR OWN AF IN REHEARSE-AF

Patients monitoring their hearts with **AliveCor Inc.**'s *Kardia Mobile* device identified more episodes of atrial fibrillation than routine care in the REHEARSE AF trial. Julian Halcox from Swansea University Medical School in Wales presented one-year data from the trial at the ESC congress on Aug 29.

The trial, co-sponsored by AliveCor and the Welsh Government, enrolled 1,003 patients 65-years or older with stroke risk-factors who were not taking anticoagulant drugs and did not have a prior diagnosis of AF. Patients randomized to the treatment group took two ECG recordings a week for a year with the Kardia Mobile device and sent them to their doctor for analysis. Patients randomized to the control group just made routine visits to local health-care providers.

During the year-long study period, 19 patients in the intervention group were diagnosed with AF compared to five in the control group even though they had similar number of risk factors. Just over 2% of the ECGs recorded and submitted were considered uninterpretable, usually due to electrical interference at the time of recording. Health economic modelling showed that each AF diagnosis in the intervention group cost around £8,255.

Most patients recording their ECGs with Kardia Mobile said they did not feel restricted or anxious about the process, while control patients reported being slightly more anxious about their risk of heart rhythm abnormalities and stroke, and frequently said they would have preferred to have been enrolled in the regular monitoring group.

"The increase in AF diagnosis with patient ECG monitoring suggests that it has the potential to reduce stroke through earlier diagnosis and treatment with oral anticoagulation," says Julian Halcox, Swansea University Medical School, Wales.

"Our study was not designed to evaluate outcomes, but the increase in AF diagnosis with patient ECG monitoring suggests that it has the potential to reduce stroke through earlier diagnosis and treatment with oral anticoagulation," Halcox said. "A much larger outcome trial is needed to evaluate the clinical impact and cost-effectiveness of this approach."

AFFIRM SHOWS BENEFIT OF BP CONTROL IN AF

A post-hoc analysis of the NIH-sponsored AFFIRM trial, presented Aug 28 by Marco Proietti from the University of Birmingham, England, shows that blood pressure control may reduce the risk of strokes and major bleeding events in patients with atrial fibrillation.

"Our findings suggest that consistency in blood pressure control, beyond the single measurement, is very important, and this appears to be the case across all types of AF patients, irrespective of age, blood pressure history, blood pressure level or clotting risk," Proietti said.

AFFIRM compared pharmacologic ventricular rate control, rhythm control, and anticoagulation in 3,843 AF patients to measure the variability in systolic blood pressure. The patients systolic blood pressure was recorded four times in the year prior to the study and then every four months after enrollment.

Over a mean follow-up of 3.6 years, the patients in the trial suffered 149 strokes and 248 major bleeding events with a clear pattern of increasing risk linked to systolic blood pressure. After adjusting for variables, the analysis showed that patients whose systolic blood pressure varied by 13.86 mmHg or more were at significantly higher risk of stroke and major bleeding than those with lower blood-pressure variability.

"The main [objective] should be to understand why these patients have the highest variability and there are several [studies] in the literature that seem to suggest that one of the main relevant issues is [the patients'] adherence to medications," Proietti said. "So before prescribing we start prescribing more drugs, that in some ways may make things worse, we should be able to be sure that our patients are taking all the patients we prescribed and at the dose we prescribed."

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J&J's Ethicon Calls For Game-Changing Holistic Approach To Obesity Care

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Researchers and surgeons from across the bariatric community gathered at the 22nd World Congress of the International Federation for the Surgery of Obesity and Metabolic Diseases (IFSO 2017) held in London, UK, between Aug. 29-Sept. 2 to discuss obesity treatment and management.

Johnson & Johnson subsidiary Ethicon, a key sponsor of the conference, took the opportunity to highlight its ongoing, multi-year, global initiative called "Project Game Changer," aimed at closing evidence gaps in obesity management and reducing clinical and economic barriers to drive greater patient access to bariatric care.

One significant barrier, the surgical device company believes, is the pervasive view among health care providers that obesity is a lifestyle condition, rather than a chronic, medical disease.

Nadia Ahmad, Senior Obesity Solutions Advisor for Ethicon, told *Medtech Insight*: "The education component is so key [and] the fundamental barrier to all obesity treatments is that we do not appreciate obesity as a disease state. We're looking at it and we're saying, 'well, the person can just eat less and exercise more and take care of themselves, why do they need costly invasive treatments?' This is a stigma and a bias that is impeding care."

"Many patients out there with obesity that need surgery and are appropriate [candidates] for surgery cannot currently get access to treatment. At present, obesity or weight issues is an area where patients really don't know where to go. This is a medical condition and a disease but most obesity 'care' is commercial [and not clinical] – it's fad diets or advice given on social media. This is a disease state where the care is largely in the commercial arena and we really need to have the care available within the health care system. There needs to be a lot of improvement on all different levels."

Ahmad said health care providers needed to be educated and trained to understand obesity from the early stages of the clinical care pathway. "We certainly need more obesity medicine specialists but we also need primary level education for diagnosis and screening. Quite simply, we need to follow the model of care that we have for other chronic diseases and build on that," she said.

Bariatric surgery, which covers a range of procedures including gastric bands and gastric bypasses, is when the digestive system is re-routed past most of the stomach. Recent preclinical research showed the surgery can alter the body's hormonal mechanisms and its ability to manage nutrients. Once hormonal triggers are reset, patients are able to achieve weight loss without fighting their own hormonal regulatory mechanisms. The procedure is considered one of the most effective solutions for sustained weight loss and obesity management but is not widely practiced.

At IFSO, Ethicon presented new data from a major retrospective study on surgical stapling, comparing economic and clinical outcomes linked to the use of either manual or powered staplers.

"We certainly need more obesity medicine specialists but we also need primary level education for diagnosis and screening. Quite simply, we need to follow the model of care that we have for other chronic diseases and build on that." Nadia Ahmad, Senior Obesity Solutions Advisor for Ethicon.

Surgical stapling devices are widely used for transection and anastomosis in both open and laparoscopic surgical oncology and bariatric procedures.

The study, "Comparison of Economic and Clinical Outcomes between Patients Undergoing Laparoscopic Bariatric Surgery with Powered vs. Manual Endoscopic Surgical Staplers", analyzed hospital discharge data from one of the largest hospital databases in the world, the Premier Perspective Hospital Database, for patients who underwent laparoscopic bariatric surgery between 2012 and 2015.

The study showed that use of Ethicon's Echelon Flex Powered Staplers was associated with significant clinical and economic benefits including a lower rate of bleeding complications and lower overall hospital costs when compared to Medtronic's Endo Gia manual staplers.

"Bariatric surgery will always remain a very effective treatment option for patients with obesity," said Ahmad. "It works really well and we know it's a safe, cost effective and life-saving procedure but we need to understand why the surgery is so effective and take that information to develop more effective therapeutics such as therapeutics that are more device based and more minimally invasive procedures or medical therapies."

Ahmad reiterated that obesity must be viewed as a disease not just because of its association with 200 other diseases, but because it is a disease causing metabolic dysfunction. "The actual accumulation of fat in a person and the maintenance of that higher fat level is caused by dysfunction in the body which is not 100% in control of the individual," explained Ahmad. "This is a fundamental concept that should change our entire approach. We should not blame people for their condition. They have a right to effective treatment and society should facilitate and advance that treatment - health is a right."

Published online 09/05/17

SetPoint Turns Up The Heat On Rheumatoid Arthritis Program

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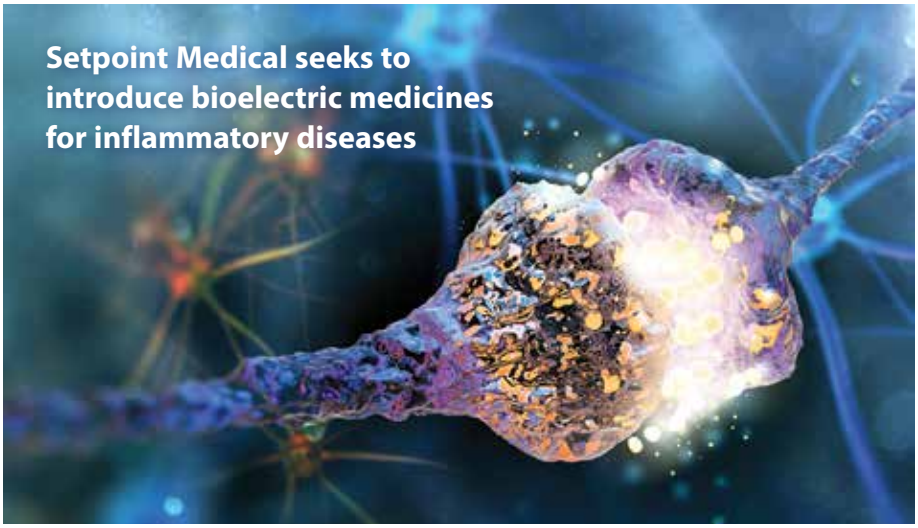
SetPoint Medical Corp. is sharpening its focus on the rheumatoid arthritis therapy market, currently dominated by biopharmaceuticals, by channeling a good part of the $30m series D financing it recently raised into a multi-center Phase II clinical trial of its vagus nerve stimulation system.

The California company's technology is a rechargeable implant the size of a vitamin pill placed on the left side of the vagus nerve. It is programmed to stimulate specific fibers within the nerve, for a few minutes once a day, which then activates the body's natural inflammatory reflex. This reflex, discovered by SetPoint's founders Kevin Tracey and Shaw Warren, creates a "biological dose" that triggers a chemical reaction to reduce inflammation and inhibit production of inflammatory cytokines for "the entire day," explained SetPoint Medical CEO Anthony Arnold.

The firm had previously conducted two small pilot studies of the technology. The first study was on patients with mild to severe RA and had not yet received any treatment with biologic agents, and the second study was on RA patients who had failed to respond to, or were no longer adequately responding to, at least two biologic agents. Of the 17 patients who took part in these studies, there were "a couple with whom we didn't get a meaningful response. But for the others, they stayed on the therapy beyond two years and all of them continue to have very good results," Arnold said.

Encouraged by the results of these pilot RA studies, SetPoint had gone on to test its technology in an eight-patient study involving another inflammatory disease, Crohn's, which is inflammation of the digestive tract. The results of the study also showed that the company's vagus nerve stimulation system was able to reduce the symptoms in six of the eight patients, and three patients even went into remission.



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However, Arnold told Medtech Insight that the firm is focusing exclusively on advancing its RA program into Phase II clinical trial, which will involve 10 to 12 centers in the US and Australia. This trial will be using the latest, "commercial-ready" version of SetPoint's vagus nerve stimulation system, which has undergone "tens of thousands of hours" of lab-testing during its development, said the CEO. The company is awaiting approval from regulators to use this new device in the Phase II trial and if it gets the green light according to plan, the trial should start later this year.

The company plans to enroll 15 patients in the Phase II to test the new device. "This is not a registration trial. It is a randomized trial to prove our device works, the physicians like it and find it easy to use," said Arnold. "This study will run about a year and hopefully, the answers we get will be 'yes, the device works well, the patients got better, the physicians like it', and then we can scale it up to a larger pivotal randomized trial to get approval in Europe and the US, get payers to pay for it and bring it to market."

However, the $30m series D which SetPoint raised in August will not take it all the way through market, but up to the point of completing the Phase II study

SetPoint Medical CEO Anthony Arnold

and getting the required positive data that will put the firm in a strong position to raise another round of financing.

With the latest $30m, the total investment in SetPoint has reached near $90m. The company's investors include industry bigwigs like **Medtronic PLC** , **Boston Scientific Corp.** and **GlaxoSmithKline PLC** (through Action Potential Venture Capital, the pharma giant's fund dedicated to bioelectronic medicines). Institutional investors include New Enterprise Association, Morgenthaler Ventures and TopSpin Partners. SetPoint's investors have proved supportive, seeing that all the existing shareholders took part in this series D round

SetPoint Medical's implantable vagus nerve stimulation device

Photo credit: SetPoint Medical

and the company would need funding for what is likely a long clinical road ahead.

Arnold conceded that for a technology like SetPoint's which is targeting a new area that other devices have not yet broken into, the journey would not be cheap. However, if the technology does prove its mettle, it could disrupt a market that is dominated by the pharma industry and help reduce health care costs for payers. According to SetPoint, over $30bn is spent annually on biologic agents to treat inflammatory diseases. However, these do not work on a significant proportion of those patients. "When you talk to most western European or US RA centers, they will say that about a-quarter to a-third of their patients either have no response or adequate response to biologics," said Arnold.

"For regulators, the risk-benefit assessment [of our technology] would be much easier because we would be helping patients with no other options. And if we can help them, we believe the uptake will be very high," Arnold said. "That's where we'll start and once we prove the efficacy of our therapy out in the market, we will be doing studies to move further up that care continuum, towards that first line treatment."

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Globus Promotes Demski To CEO

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Globus Medical has promoted its president of emerging technologies, David Demski, to the role of CEO. Demski succeeds and will report to David Paul, who has been chairman and CEO of the Audubon, Pennsylvania-based orthopedics company since he founded it in 2003. Paul will remain in the role of chairman and focus on strategic initiatives, but will delegate less time on day-to-day operational matters. These changes in management responsibilities will allow Paul to recover from a health condition, according to Globus Medical.

Demski has also been with Globus since its inception, first serving as chief financial officer for five years, before becoming president and chief operating officer in 2008. In 2015, he took on the role of president of emerging technologies.

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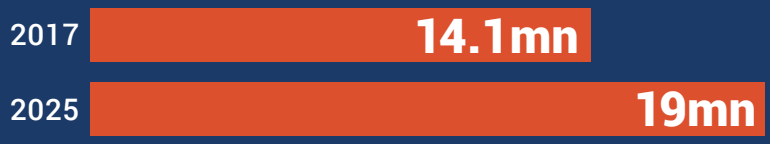
Biopsy Device Market Size To Exceed $2.3bn By 2021

Increased rates of cancer are predicted to drive growth of sales of biopsy devices from approximately $1.6bn in 2016 to an estimated $2.3bn in 2021. The US currently holds the largest market share but sales in the rest of the world (RoW) is expected to experience the largest amount of growth over the forecast period.

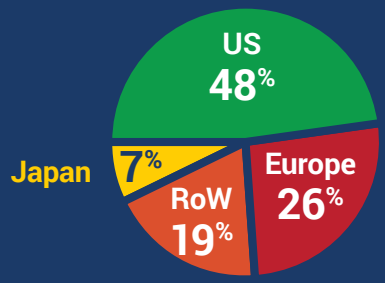
6.7%

Projected compound annual growth rate of biopsy device sales worldwide

NEW CASES OF CANCER DIAGNOSED GLOBALLY
(excluding non-melanoma skin cancer)



(Centers for Disease Control and Prevention, 2017)



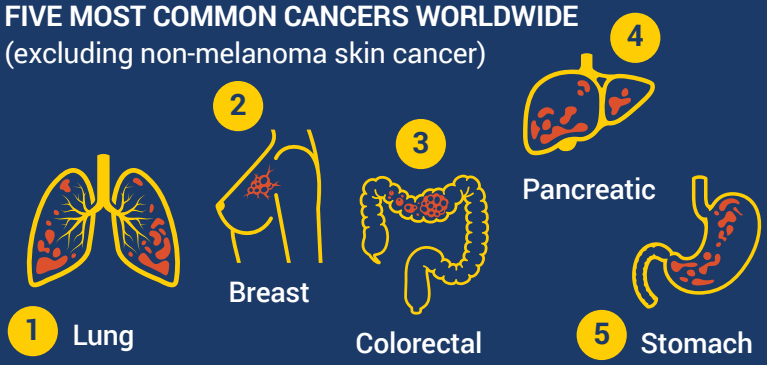
GLOBAL BIOPSY DEVICES MARKET
SHARE BY COUNTRY/ REGION, 2016

$1.6bn 2016

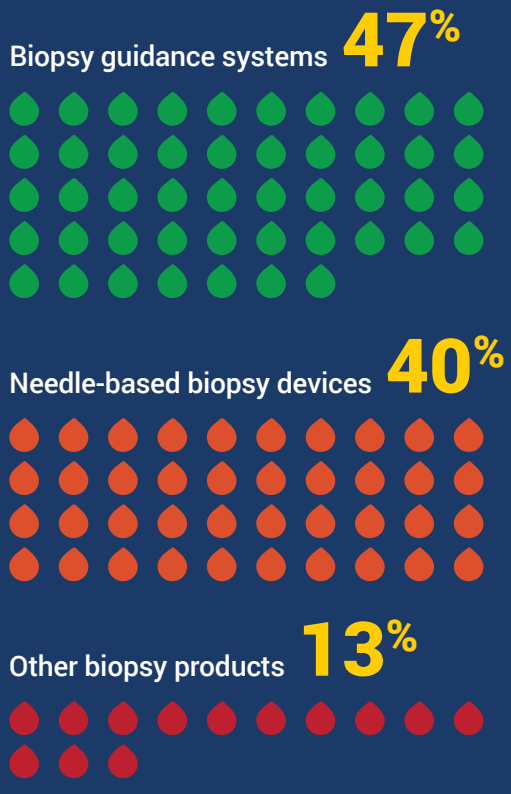
GLOBAL SALES OF BIOPSY DEVICES

$2.3bn 2021

FIVE MOST COMMON CANCERS WORLDWIDE
(excluding non-melanoma skin cancer)



GLOBAL BIOPSY DEVICES MARKET,
SHARE BY PRODUCT TYPE, 2016



Source: Meddevicetracker's Biopsy Device Market Report

Mainstay Taps Ex-NuVasive President, COO To Succeed Crosby

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Mainstay Medical International PLC has appointed Jason Hannon, former president and COO of spinal device manufacturer **NuVasive Inc.** , as the successor to Peter Crosby, who is stepping down as CEO to go into retirement. The appointment will be effective from Oct. 9; Hannon will also take a seat on the board of directors. Hannon left NuVasive in July, after 12 years at the company where he held various senior executive roles with responsibilities including overseeing the growth of NuVasive's international operations, business development and strategy, before becoming president and COO in September 2016.

During his time at the helm of Mainstay, Crosby has taken the company through an IPO, CE mark approval of its ReActiv8 neurostimulation system and the first sale of the device in Germany. The Dublin, Ireland-based firm is now looking to accelerate commercialization of ReActiv8, which electrically stimulates and strengthens the nerves responsible for contracting the key muscles of the lumbar spine to restore functional spine stability.

In its first-half 2017 results, the company posted revenue of $0.25m, while increased investment in clinical and commercialization activities led to a widening of net loss to $12.3m (vs $8m in H1 206). The company had $24.5m available cash as of June 30, 2017. The firm said it will have sufficient funds to be able to meet its liabilities as they fall due for a period of at least another 12 months.

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Guerbet Names New Chief Digital Officer To Lead Innovation

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French medical imaging specialist **Guerbet SA** has appointed François Nicolas Chief Digital Officer (CDO).

In this newly created role, Nicolas will lead the company's innovation strategy as it focuses on accelerating growth in digital services for diagnostic and interventional solutions. This appointment follows the nomination of digital technology experts, Thibault Viort and Eric Guerbert, to Guerbet's board of directors in May 2017.

Nicolas has over 20 years of experience in the design and development of biomarkers and health solutions using digital health technologies. He spent 15 years with GE Healthcare in various leadership roles, including Neurology PET director and Biosignature Technology leader. In the latter role, he led a cross-company initiative to define a multi-modality diagnostic funnel for Alzheimer's disease, according to his LinkedIn profile.

In addition to this, Nicolas served as the vice president of Sanofi's Diabetes Integrated Care division, where he was the business lead representing Sanofi during the creation of its strategic partnership with Google Life Sciences (now called Verily).

Prior to joining Guerbet, he was chief operating officer of a start-up called Impeto Medical, which was developing diagnostic devices for peripheral small fiber neuropathies.

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New Head For SymCel To Push Commercial Phase

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SymCel Sverige AB, a specialist calorimetry-based diagnostic solutions, has appointed Jesper Ericsson CEO. He succeeds Christer Wallin, who has been at the helm of the Swedish firm for the last six year and is now retiring. Ericsson joins SymCel from BioLamina AB, a manufacturer of cell culture reagents, where he was responsible for global sales, both direct and through distributors. His experience in commercializing cell-based products will stand him in good stead to accelerate sales of SymCel's calScreener, a technology for measuring metabolic activity in live material, such as cells, bacteria or even a parasite. The company has been selling the technology to the research market since 2014 and plans to move into the clinical diagnostic market, especially for microbiology applications. *(Also see "Symcel Nabs SEK5.6m To Take Calorimetry Tech Into Medical Dx " - Medtech Insight, 24 May, 2016.).*

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CONTINUED FROM PAGE 1

be felt by some specific review divisions more than others.

In issuing the July exemption notice for class II devices, FDA identified 244 device product codes slated for full 510(k) exemption. In addition, there were 93 additional examples of partial exemptions. For this analysis, we focused on the 244 full exemptions.

Of the 244 product codes, 85 had previously (in a 2015 guidance document) been tapped by FDA for 510(k) exemption, but had yet to be made official. The Cures mandate triggered the agency to add 159 more codes to exempt. Of the 244 exemptions, 46 codes do not have *any* cleared 510(k)s where they are the primary code. And 50 devices are under an "enforcement discretion" policy, which means that FDA has chosen to not enforce some or all the regulatory requirements for those devices.

But, certainly, there have been thousands of 510(k)s cleared since 1976 among the newly exempted product codes. Below, we assess, in five graphics, what the 510(k) review and clearance trends – as well as registration and listing data – say about the likely impact of the recent exemptions.

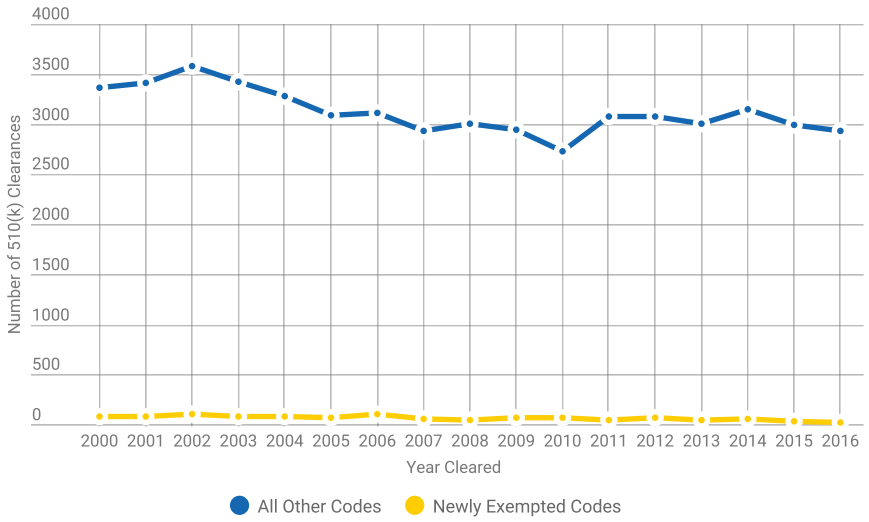
510(K)S WERE DECLINING, BUT REVIEW TIMES NOTHING TO SNEEZE AT

Among the newly exempted product codes that are linked to 510(k)s, there have 4,378 clearances from 1976-2016. More than 60% (2,780) of those clearances happened before 1996, and, as shown in Figure 1 (*See cover.*), the number of clearances has steadily declined in recent years, to only 25 in 2016. This reduction likely represents a decline in innovation and/or modifications made to products within these codes, among other possible factors. Of note in this context, 27% (66) of the newly exempted 244 codes *did not* have active device listings on FDA's registration and listing database in 2016.

In all years, the proportion of 510(k)s cleared in the exempted code categories compared to the total number of cleared 510(k)s is very small, as shown in Figure 2; for instance, 0.85% in 2016.

FIGURE 2

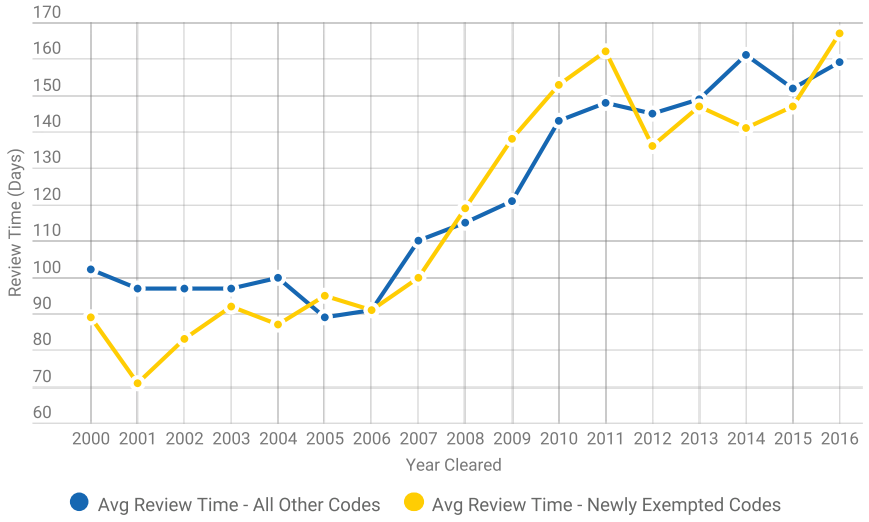
510(k)s Cleared Per Year, Newly Exempted Vs. All Others



Source: Graematter Inc.

FIGURE 3

Average 510(k) Review Days - Newly Exempted Vs. All Others, 2000-2016



Source: Graematter Inc.

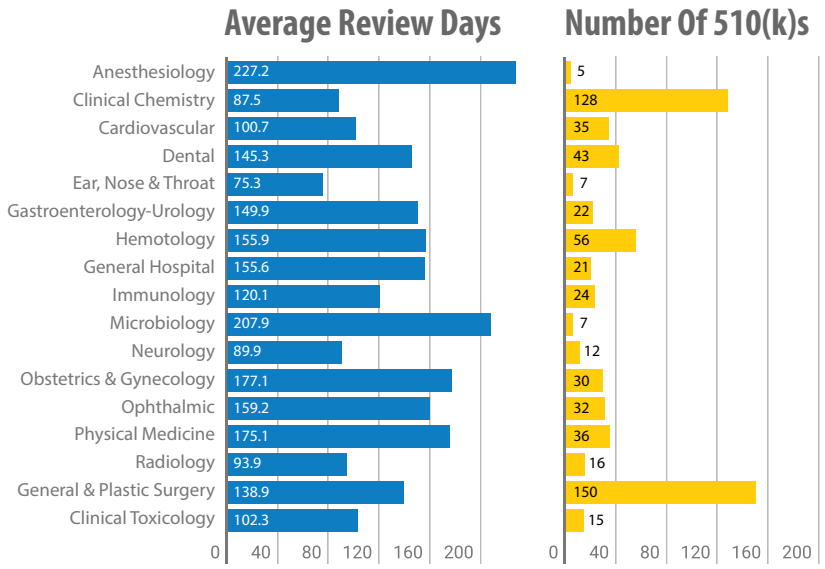
Interestingly, though, while the 510(k) numbers already dropped before the formal exemptions were announced, the average review times for this mix of products had not declined. The time it took, on average, for FDA to review devices in the now-exempted categories has consistently aligned very closely to overall 510(k) review-time averages, as illustrated in Figure 3.

510(k) reviews for exempted products actually took about seven days longer, on average, than reviews for all other products in 2016, even though the exempted devices have now been found by FDA not to require a 510(k) submission to assure safety and effectiveness. This suggests there could be some individual cases where meaningful resources are freed up for a reviewer to spend time on higher-risk devices.

The extent of the impact is likely to depend on the clinical classification of the device. As shown in Figure 4, 510(k)

FIGURE 4

Average Review Time And 510(k) Numbers For Newly Exempted Codes, By Review Committee, 2006-2016



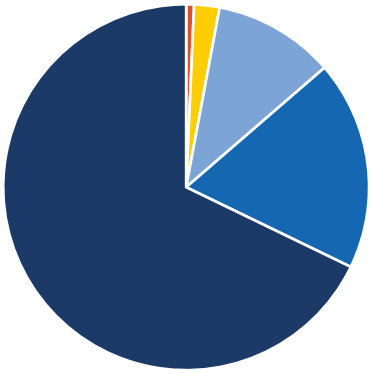
- Anesthesiology (AN) had the highest average review times for the fewest number of 510(k)s (5).
- Ear, Nose, & Throat had the fastest review time average, but only 7 510(k)s cleared.
- Clinical Chemistry (CH) and General & Plastic Surgery (SU) had the most number of 510(k)s.

Source: Graematter Inc.

FIGURE 5

Proportion Of Company Portfolios Now Exempt

Based on an analysis the newly exempted codes cross-referenced to FDA's Medical Device Registration & Listing Database



- 38 Owners/Operators have newly exempted codes as >60% of their portfolio
- Majority of Owners/Operators have newly exempted codes as 20% or less of their portfolio

81-100% 61-80% 41-60% 21-40% 1-20%

Source: Graematter Inc.

clearances granted over the past decade for devices in the exempted categories fell into 17 different review advisory committee categories. Of those, most saw less than 50 clearances during the 2006-2016 period. But two clinical categories stood out as having the most activity and, thus, the most to gain from the exemptions.

Clinic Chemistry was the most common category in terms of the number of exempted codes, and second in number of 510(k)s (128). General & Plastic Surgery, meanwhile, had 15 fewer codes on the exempted list, but 22 more 510(k)s (150) during the 2006-2016 period.

Anesthesiology devices were distinguished by having the highest average review time for the fewest number of 510(k)s (five). Ear, Nose, & Throat products, meanwhile, had the fastest review time average, but only seven 510(k)s cleared.

A FEW FIRMS WILL SEE SUBSTANTIVE CHANGE

A more direct way to assess industry impact is to look at the proportion of companies that have developed products in the exempted categories. This was done by cross-referencing FDA's device registration and listing database with the exempted-code information.

Of the total number of owner/operators registered with FDA, about 6% included devices in the exempted categories among their products. Of those 1,305 companies, only 38 of them have newly exempted codes as greater than 60% of their portfolio. Newly exempted devices account for less than 20% of products for a significant majority of the relevant owner/operators, as illustrated in Figure 5.

These most recent exemption listings, while moderate in impact on their own, are not isolated actions. They fit with a trend for an agency that is by-and-large moving in the direction of streamlined requirements and more transparency, both at the direction of the Cures Act and independently.

The Cures Act requires FDA to publish new lists of exempted devices at least once every five years. There currently remain 154 class I devices that have a 510(k) requirement, 41 more that are under an enforcement discretion policy, and 139 class II devices that reside under enforcement discretion. These devices may serve as low-hanging fruit for the agency's next round.

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Applying Real-World Device Data: US FDA Finalizes Its Thoughts

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Real-world device data may be suitable to support clearance or approval of a new device or expanded indication, but controls to mitigate bias and ensure data is sufficiently relevant and reliable are a must, US FDA conveys in a final guidance posted Aug. 30.

The final "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices" tracks very closely to a draft version issued in July 2016, but it includes some more explicit statements supporting application of real-world evidence (RWE) as a regulatory tool, particularly in support of pre-market submissions. The final version also includes some additional examples describing potential use of real-world data, new factors needed to consider the relevance of real-world data, and more term definitions.

RWE is a cornerstone of the device center's strategic priorities. The center is working closely with outside collaborators to develop the National Evaluation System for health Technologies (NEST), intended as a shared network of data collected from routine clinical care via registries, insurance claims, health records and other, particularly electronic, sources, that can support a range of decisions tied to the use of medical devices. *(Also see "NEST Executive Director: A One Woman Army" - Medtech Insight, 19 May, 2017.)*

Although the concept was originally formulated for post-market surveillance, focus on its prospective role as a tool to accelerate pre-market development has steadily increased. The recently enacted MDUFA IV user-fee agreement designates some fee revenue to building NEST and running some initial pilot studies to assess its use to support pre-market submissions. *(Also see "Pilot Of New US Evaluation System Will Include At Least Two Devices" - Medtech Insight, 31 Oct, 2016.)* The FDA Reauthorization Act, which included the MDUFA deal, also requires FDA to run post-market surveillance projects using NEST. *(Also see "MDUFA IV (And More) Is Law: Trump Signs A Health-Care Bill" - Medtech Insight, 18 Aug, 2017.)*

The newly finalized guidance is intended as user guide, of sorts, for these efforts, explaining when so-called real-world data of the type that will be collected by NEST can be rightly be considered RWE that provides valid scientific evidence to support a regulatory decision. The document details what specific types of decisions and efforts RWE might support; what assessments and controls must be considered when weighing whether it is appropriate to use RWE instead of, say, relying on more traditional clinical trial data collection; and other issues, such as when an investigational device exemption might be a necessary prerequisite to collecting real-world data.

Much of this was laid out in the draft guidance last July. As with that version, FDA differentiates between the terms "real-world data," which is routine-care data derived from various sources, and "real-world evidence," which is clinical evidence derived from the analysis of real-world data. *(Also see "FDA Moves Real-World Evidence Paradigm Forward With Draft Guidance" - Medtech Insight, 28 Jul, 2016.)*

> The final guidance includes some more explicit statements supporting application of real-world evidence as a regulatory tool, particularly in support of pre-market submissions.

The final document reemphasizes that nothing in the guideline is meant to lower regulatory standards. "This guidance should not be construed to alter, or change in any way, the existing evidentiary standards applicable to FDA's regulatory decision-making," the guidance states. "Rather, it describes the circumstances under which RWD [real-world data] may be used to support a variety of FDA decisions based on the existing evidentiary standards."

The updated guidance, though, does include some revisions. Of note, there are several spots that appear more explicit in describing the breadth of pre-market applications of real-world data. For instance, while the "background" section of the draft guidance emphasized use of RWE to support the "expansion of indications for use of cleared or approved devices," the final version added that it "may be suitable to support the clearance or approval of a new device." In listing examples of purposes of real-world data, the final guidance explicitly added its potential as evidence to support approving a humanitarian device exemption, PMA or *de novo* request, as well as evidence to support a device reclassification or biomarker validation.

From a substantive standpoint, though, there might not be much of a shift here. The draft and final documents closely align on some specific examples offered for application of RWE, including, for instance, relying on an existing, ongoing registry as a concurrent control group, rather than enrolling and randomizing a control group, to support approval of a new device.

The final guideline details a series of other use examples, like the draft version, but with more specifics added in some cases. The guidance, for instance, notes that real-world data "collected using a randomized exposure assignment within a registry can provide a sufficient number of patients for powered subgroup analyses, which could be used to expand the device's indications for use."

The guidelines also discuss FDA's experience with companies and provider groups developing patient registries to satisfy post-market surveillance "Section 522" orders or to support post-market conditions of approval. It also discusses real-world data as potentially useful as supplementary data to determine how to respond to potential safety signals from a device, and to establish objective performance criteria and performance goals.

WHEN IS RWE SUFFICIENT?

Another central goal of the guidance is to describe when real-world data is suitable to support regulatory decisions, which, the agency emphasizes, is always going to be a case-by-case consideration that often will be facilitated with the device center's pre-submissions process. Particularly for registries or other datasets that already exist, it's not guaranteed that data is being collected in a manner to meet a company's particular regulatory needs.

It's possible to use either retrospective or prospective real-world data, but "to mitigate potential bias, careful study design is needed, and a study protocol and analysis plan should be created prior to accessing, retrieving and analyzing" real-world data, FDA states.

When assessing the suitability of data, FDA says sponsors must assess both its relevance to the specific regulatory questions at hand and the reliability of the data. The final version of the guide adds a more detailed, though non-exhaustive, list of 16 factors FDA might weigh in determining the relevance of real-world data. Factors in include whether the data contains sufficient details; the overall percentage of patient exposure to the studied device that is captured in the data source; and whether sufficient data elements are collected to adjust for confounding factors.

In addressing factors to judge reliability, FDA basically maintains the approach it set out in the draft guidance, with factors listed to assess if a data source appropriately captures data accrual and if appropriate quality control measures are in place. One difference is the final document leaves out one factor for judging data-accrual methods that was found in the draft: "whether the act of collection of data impacts the ability to measure treatment outcomes."

The final guidance also explicitly defines additional terms, including "interventional study," "large simple trials" and "post-market surveillance."

FDA Commissioner Scott Gottlieb highlighted finalization of the guidance as an important development for the agency.

"Our aim is to encourage the development and use of real-world evidence gleaned from actual use by advancing these expanded recommendations for device manufacturers and the medical community," Gottlieb said. "Greater use of real-world evidence can help devices come to the market faster and expand the depth and reliability of the information we have to inform the safe and effective use of new products."

"Greater use of real-world evidence can help devices come to the market faster and expand the depth and reliability of the information we have to inform the safe and effective use of new products," FDA Commissioner Scott Gottlieb says.

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Industry Issues Guidelines To Head Off Potential CDS Software Regs

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A new set of guidelines published by the industry Clinical Decision Support (CDS) Coalition is meant to head off any potential regulations from FDA, even following enactment of provisions in the 21st Century Cures Act that limits the federal regulator's authority in overseeing such technology.

The CDS Coalition guideline outlines voluntary measures manufacturers of medium-risk CDS software could take when designing their product to ensure a level of trust in the products and manufacture practices in the hopes that FDA will stay out of regulating the area.

Under the Cures Act passed last year, FDA cannot regulate administrative-support software, such as those used to process financial claims and provide patient data for administrative purposes. Software used to encourage healthy lifestyle, electronic patient records and those to display clinical laboratory tests or other device data are also generally exempt from FDA oversight. *(Also see "'Cures' Bill Circumvents FDA On Medical Software Regs" - Medtech Insight, 30 Nov, 2016.)*

For several years now, FDA itself has made it clear through several policy documents and guidances that it will use a risk-based approach to such products and, for the most part, refrain from regulating the sector.

In fact, the agency has already stated and the Cures Act reinforced the notion that regulators would only oversee high-risk CDS software. Recently, FDA has even announced plans to develop a pathway for software qualifying as a regulated medical device that reduces pre-market requirements based on trust in a manufacturer's processes. The Digital Health Precertification Program is being tested in a pilot project and has received high praise from groups including the CDS Coalition. *(Also see "Industry Praise US FDA Software Pilot Program" - Medtech Insight, 31 Jul, 2017.)*

However, neither the Cures Act nor FDA's more relaxed approach to the technology has fully satisfied software developers, including members of the CDS Coalition, which argues there is still a lot of ambiguity around what kinds of software the agency will consider regulating. In particular, the group points to some gray zone in what is considered a high-risk product versus a medium-risk product.

FOCUS ON MEDIUM-RISK CDS

The new document outlining voluntary guidelines companies should take is intended to fill in some of the gaps left by the Cures Act by focusing on medium-risk CDS software in a bid to dissuade the agency from regulating such products.

"As a result of the 21st Century Cures Act, certain CDS software will not be regulated by FDA," said the industry lobby group. "The exact line drawn by the statute will need to be interpreted by FDA, and we want to give FDA confidence that for that software the agency does not regulate, industry will do an adequate job of self-regulation."

The coalition says the Cures legislation "provides an avenue for FDA to claw back into regulated territory any software that the agency finds may lead to serious injury or death in patients. If industry does an adequate job of self-regulating and therefore avoiding such patient injury, industry can reduce the likelihood that FDA will need to expand the scope of its regulation."

According to the CDS Coalition, the guidelines are meant to create a unified approach to giving a basic level of transparency on how CDS software is designed and, at the core, is intended to let software developers figure out if additional validation is needed to support the software taking over some of the clinical decision-making duties from health-care providers.

> "If industry does an adequate job of self-regulating and therefore avoiding such patient injury, industry can reduce the likelihood that FDA will need to expand the scope of its regulation," the CDS Coalition says.

The group emphasizes the guidelines are voluntary and not prescriptive, but they are recommended to provide a potential "safe harbor" for companies from FDA oversight. Products that do not meet the guidelines are more likely to rely more on their proper function over the judgment of the health-care providers who use them, and could require more validation and lead to the FDA stepping in to investigate.

"These guidelines reflect the view that taking over, in any substantial way, the health-care decision-making carries with it heightened responsibility for validation," states the coalition. "Software that does not meet these guidelines can be quite safe and effective, but may require additional validation because of the risk that such software will supplant the judgement of health-care professionals."

When complying with the guidelines outlined by the CDS Coalition, the group says developers of the products need to ask two fundamental questions:

- Are health-care professional users able to independently review the basis of the recommendations the software makes? and,
- Under the intended circumstances of use, will health-care professional users not need to rely primarily on the software?

Ultimately, the goal of the guideline is to help CDS software developers meet certain criteria that will signal to health-care providers and FDA that they have done their due diligence to make sure that different use scenarios have been considered and risks to patients have been minimized.

SOFTWARE TRANSPARENCY HIGHLIGHTED

Among the considerations highlighted in the guidelines is transparency, so that health-care providers can independently review clinical-decision recommendations made by the software to know the process is sound and have enough time to look over how the software came to its recommended decision.

Other recommendations made in the guideline include ensuring software is handled by competent users who have necessary training and authority to use it, and that the labeling of the product reflects that.

"To qualify as intended for use by people who can act as competent human intervention, the labeling should elaborate on the limits of what the software itself can do, and the need to go beyond the software in certain cases," says the coalition. "Further, if a decision informed by the recommendation of the software could lead to serious injury, permanent impairment or death for the patient, the labeling should also be clear about the necessary qualifications of the intended user."

The coalition also states in the guidelines that promotional practices by manufacturers should reflect the software is intended to be used by intended users, which means the sales and marketing of such products should only be targeted at such users.

The CDS Coalition says it will periodically look over its guidelines and update them as the need arises based on what they learn from industry, and as the technology changes. The coalition was specifically created to lobby Congress and FDA to take a more hands-off approach to CDS software, a goal it seems to have largely accomplished with the Cures Act and FDA's insistence on only regulating high-risk products.

"The CDS Coalition is a temporary coalition created to seek improvements in the regulatory environment for clinical decision support software," states the guideline. "As a consequence, the Coalition's objective will be to find a permanent organization that is interested in keeping these guidelines up-to-date in the future. We shall be actively looking for such an organization over the next year, and transfer that responsibility to the new organization once we identify it."

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Moonshot Projects In Life Sciences Strategy Can Lift UK Over Brexit Hurdle

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The means to secure economic growth for the UK life-sciences industry over the next 15-20 years have been laid out in the UK's Life Science Industrial Strategy report, released today. Developed in consultation with the Life Sciences Industrial Strategy board, the strategy was commissioned by a reshuffled Conservative government in the wake of the 2016 Brexit vote.

Author of the report, Professor Sir John Bell, Regius professor of medicine at Oxford University, wants the UK to invest in high-risk life sciences "moonshot" projects in the hope of creating some entirely new industries during the next 10 years.

Bell's report covers all the UK life sciences, and has had input from across the industries – from major pharmas such as AstraZeneca, Johnson & Johnson and GSK, as well as associations and companies large and small in the medtech and diagnostic sectors. Health and industry ministers worked closely on the recommendations in the report, which complements the objectives set out in the NHS's Five-Year Forward View. *(Also see "UK Viewpoint: Tech & Innovation In Focus In NHS Chief's 'Forward View'" - Medtech Insight, 31 Mar, 2017.)*

Speaking today, Bell, who is also chairman of the Office for the Strategic Coordination of Health Research, said it is important to identify areas of the life sciences that are likely to expand dramatically in the coming years. That calls for a "thought experiment" that envisions both what healthcare will look like 20 years from now, and how to build corresponding industries that will help the UK dominate in those sectors.

One of the report's recommendations is to build expertise in artificial intelligence (AI) and machine learning to transform pathology and imaging. Others focus on genomics, maximizing the work of the UK Biobank and Genomics England, and on diagnosing chronic diseases asymptomatically. Bell acknowledges that there should be a readiness to co-develop themes where some life science and wider industrial strategy elements might overlap, for instance in the field of AI.

Shutterstock: Stefan Schurr

Business secretary Greg Clark also today announced an initial £146m ($188m) investment in the sector to set up five new UK life science research centers over the next four years, and to support innovation in manufacturing, advanced treatments, and SME R&D. They five projects are:

- Establishing an advanced therapies treatment center to help deliver cell and gene therapies to a larger number of patients (a £30m investment in three new sites to build a network of centers based in hospitals).
- Expanding the Cell and Gene Therapy Manufacturing Centre with and extra £12m to double the capacity of the Cell and Gene Therapy Centre in Stevenage *(Also see "Killer Cures: Industry Heavyweights Make Their Presence Felt In Cell And Gene Therapy" - Medtech Insight, 19 Jun, 2017.)*
- Setting up a medicines manufacturing innovation center (a £13m competition will be run to establish a new center in partnership with industry that will accelerate the adoption of emerging and novel manufacturing technologies).
- Investing £66m in a new center of excellence for vaccines development.
- Allocating £25m to support SME R&D, innovation and manufacturing.

ADVANCED UK RESEARCH BODY

The life sciences plan is the first of five sector reports commissioned by the UK government following the launch of the industrial strategy green paper. In it, Bell proposes closer government-industry-provider collaboration. A new Health Advanced Research Programme (HARP) body will be tasked with maximizing government and industry funding links.

HARP would act as a host body for public, charity and corporate funders wishing to undertake the necessary large, well-resourced research infrastructure projects that Bell wants the new strategy to provide for. Each of these would require several hundred million pounds in investment.

Five Key Themes Of UK Life Science Strategy

The strategy seeks to address the following challenges:

- **Science** – Supporting the science base, maintaining strength and international competitiveness.
- **Growth** – Creating an environment that encourages companies to start and grow, building on strengths and expanding the manufacturing sector.
- **NHS** – Collaborating with industry and adjusting to ensure better adoption of innovative treatments and technologies by recommending the Accelerated Access Review (AAR) be adopted with national routes to market streamlined and clarified, including for digital products.
- **Data** – Making best use of digital tools and sources to support research and patient care –such as X-rays and digitized pathology samples, and developing AI protocols. Up to five Digital Innovation Hubs are to be set up, with ABHI noting that at least one will be focused solely on medtech.
- **Skills** – Ensuring access to talent via a strong skills strategy: special efforts must be made to attract and retain highly-skilled workers from the EU and elsewhere. One strategic goal is to attract 2,000 new discovery scientists from global pharmaceutical companies to the UK over the next five years,

FASTER ACCESS TO INNOVATIVE TECHNOLOGY

Strategy proposals on faster availability of innovative technologies for patient care are key for the UK medtech industry. The report calls for the NHS to accelerate access to such technologies by streamlining new product assessments, with NICE playing a key role. The issues of pricing are not included in the scope of the report.

The aim is for the NHS to engage in some 50 collaborative programs with industry during the next five years, in late-stage clinical trials, large-scale data analysis and evaluation of medical devices and diagnostics. These are likely to be very specific transformational innovations, but the 15 AHSNs (and their new Exchanges) will also offer an industry channel for innovation adoption. *(Also see "UK Viewpoint: AHSNs, AAR And Accelerators – Market Access & Innovation Update" - Medtech Insight, 17 Aug, 2017.)*

Health secretary Jeremy Hunt is also announcing £14m funding to support 11 medical technology research centers to encourage collaboration between the NHS and industry. These will develop new technologies through the National Institute for Health Research (NIHR).

NHS – AN UNDERUSED TOOL

Bell stresses the vital strategic nature of the NHS, whose resources need to be better used to make the UK a global draw for research projects and input. In the introduction to the report, he says that the strategy's agenda is "central to ensuring and improving [the NHS] for future generations." Many of the steps outlined in the strategy are opportunities uniquely available to the NHS and could not be realized in many insurance-based healthcare systems, he wrote.

Besides closer collaboration between industry and the NHS, other key recommendations of the report include better incentives for companies to invest in UK manufacturing, and action to shore up skills shortages.

MEDTECH INDUSTRY SEES GOOD POTENTIAL IN BELL REPORT

The importance of increased collaboration with the NHS, emphasized throughout the document, is acknowledged by the Association of British Healthcare Industries in a statement. But it also recommends that for NHS-industry partnerships to succeed, and to address the UK's long-standing challenge of adopting new technologies, "the recommendations of the Accelerated Access Review must be rapidly implemented." £86m of government funding was recently granted as an interim step under the AAR.

Separately, the association is working with the Office of Life Sciences (OLS) to reconstitute a formal Ministerial MedTech Forum that brings together all stakeholders, including the NHS.

Generally, the ABHI sees much to applaud in the Bell report's positive recommendations for the medtech industry. Proposals to strengthen clusters will aid the growth of the local industry, it says; it also suggests that further investment is needed in export campaigns that support UK medtech SMEs.

Plans to provide support for four to six single medtech or diagnostic domains, in areas such as orthopedics, cardiac, digital health, or molecular diagnostics are also welcomed by industry. They would allow the UK to develop globally-leading expertise centers and ideally make them magnets for global inward investment from major medtech partners.

NEXT STEPS – CONTINUITY & THE LONGER-TERM APPROACH

While all economic activity in the UK remains under the shadow of Brexit and its as-yet-unknown connotations, the drive of the UK life sciences industry generally – and as stated explicitly in the strategy report – is for the UK to remain as closely involved as possible in EU regulatory systems. This convergence is supported by the ABHI.

Bell wonders, "Can we establish a regulatory system that is aligned with what goes on in Europe?" while acknowledging that Brexit, to some extent, will determine the success of his Life Sciences Industrial Strategy.

The next task is to secure a sector deal, and Bell notes that it is the view of industry that the strategy should be viewed over at least a five-year period – not as a moment in time when a sector deal is agreed. Over this period, there will be a need for oversight of the program as the strategy "emerges as a dynamic set of actions and outcomes for the economy, industry and the NHS."

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UK Regulator Seeks To Ease EU MDR/IVDR Navigation With Interactive Guide

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The UK Medicines and Healthcare products Regulatory Agency has published an interactive guide to help device and IVD firms navigate obligations under the new EU regulations governing medtech.

The guide comprises a 27-page, interactive PDF that introduces readers to the new requirements and contains hyperlinks to relevant external resources. It is designed to help experienced manufacturers navigate the increased requirements for devices and diagnostics, as well as those companies who will be new to medtech regulations as a result of the broader scope of the new rules, the MHRA said.

The Medical Device Regulation (2017/745) and IVD Regulation (2017/746) came into force on May 25 and, following transition periods, will fully apply across the EU starting on May 26, 2020, and May 26, 2022, respectively. During the transition periods, products can be placed on the market under the current EU directives governing devices and IVDs, or under the new regulations.

The interactive PDF covers the range of obligations involved in manufacturing and supplying products under the MDR and IVDR. The regulations include clearer obligations for industry, a greater emphasis on traceability throughout the whole supply chain with the introduction of a unique device identification system, and new standards for clinical evidence, the MHRA noted. They also set out more rigorous vigilance reporting requirements, including new reporting timescales, as well as clearer requirements on what a manufacturer's post-market surveillance system should comprise. (*Check out synopses of key chapters of the new regulations on our EU Regulation Recap page.*)

Among other things, the guide briefly explains what requirements must be met for a conformity assessment. For example, it explains that Annex I of the MDR and IVDR provides information on general safety and performance requirements. It talks about the need to provide clinical evidence and investigation to prove that the benefits of a product outweigh its risks and that the product achieves its claimed performance.

Information on technical documentation requirements can be found in Annex II of the regulations, while information about harmonized standards/common specification can be found in Articles 8 and 9 of the MDR and IVDR.

The instances in which a device can be placed on the market without undertaking an assessment of conformity are also addressed in the guide. For instance, this might be the case when quick market access is in the interest of public health or patient safety or health, the guide says. It adds that Article 59 of the MDR and Article 54 of the IVDR provide more information on when it is possible to derogate from the conformity assessment procedures.

The guide also deals with "borderline" products that are difficult to identify as a medical device or medicine. In addition, it contains highlights six groups of products that do not have a medical benefit – such as dermal fillers and non-corrective contact lenses – but which are now regulated as medical devices under Annex XVI of the MDR. Manufacturers of products listed in Annex XVI must comply with common specifications that are expected to be published by the European Commission by 2020, the guide notes.

"We live in an increasingly digital world, and the way we provide our guidance is changing," the MHRA's director of medical devices, John Wilkinson, said of the interactive guide. "We want to help manufacturers to comply with the new regulations as easily and as early as possible," he added.

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EU Extends Deadline For Comments On Review Of Tissues And Cells Legislation

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The European Commission has extended the deadline for stakeholders to respond to a consultation on whether the current EU legislative framework for blood, tissues and cells is fit for purpose or whether developments in science and technology, the arrival of for-profit companies, and new disease transmission risks mean that the rules need to be overhauled.

Among the issues under review is whether the legislation is still adequate to regulate situations where tissues and cells are used as starting materials for the manufacture of medicines or medical devices.

This is the first formal evaluation of the legislation since the basic directives on blood, tissues and cells were adopted in 2002 and 2004. It consists of several steps including a roadmap, a study commissioned from an external contractor, and a public consultation process that began on May 29 and was meant to end on Aug. 31 but has been extended by two weeks to Sept. 14 "at the request of a number of stakeholders," the commission says.

The aim of the consultation is to gather factual information on "what works well" and where there is room for improvement, and on the impact of the legislation. As well as the online public consultation, meetings are being held with stakeholders to "gather focused/specific input through direct interaction. The plan is to publish the final evaluation report by the end of 2018.

The roadmap, which was put out for comment until Feb. 15 this year, noted that the directives have not been evaluated since their adoption "despite a considerable degree of scientific and technological development in the sectors and new risks of transmitting emerging diseases."

It also pointed out that the sector is undergoing "organisational change including the market entry of private operators (commercial/for profit companies) into a traditionally non-profit oriented sector with mainly public actors."

Among the questions being asked of stakeholders in the present consultation are:

- Is the legislation sufficiently up to date and in line with scientific, technical and epidemiological developments and innovation?
- Is it adapted to other changes in the sector such as commercialization and internationalization?
- Are the requirements of the EU directives suitable when blood, tissues and cells are used as starting materials for the manufacture of medicinal products/medical devices?
- To what extent is the legislation coherent with other relevant international/third country approaches to the regulation of the quality and safety of blood and tissues and cells?

STAKEHOLDER EVENT

A stakeholder event is being held in Brussels on Sept. 20 to allow the public, national authorities, patient and donor groups, professionals and other relevant groups to exchange views. Topics will include regulatory oversight (covering inspections, authorizations, vigilance and traceability), consistency with other EU legislation, and factors such as changing risks, biotechnological innovation, globalization and commercialization.

The event will be used to "validate the findings of the open and targeted consultation activities and to plug any remaining evidence gaps," the commission says.

The study supporting the evaluation is being prepared by ICF Consulting Services Ltd, a company that the commission says has conducted several other evaluations of the EU legal framework in the area of health and food safety. Experts in blood, tissues and cells are being subcontracted to support the evaluation work.

The study will be based on documents and reports including those from the European Parliament, the Council of Europe and the World Health Organization, as well as published literature and the results of the public and targeted consultations.

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CMS Advisors Say More Evidence Needed For Obesity Surgery

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It's not clear whether surgical obesity treatments offer much benefit to Medicare patients, a panel of advisors concluded Aug. 30. But rather than close the door on coverage entirely, several members of the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) suggested the program should cover the surgeries in a clinical trial context while more data specific to Medicare patients is collected.

The panelists suggested the US Centers for Medicare and Medicaid Services take a step known as coverage with evidence development, which allows reimbursement for items and services if they are provided as part of approved clinical studies, or with the collection of additional clinical data.

"Coverage with evidence development could be very helpful," said Doug Campos-Outcalt, medical director, Mercy Care Plan. "Without coverage, we won't get the data. If we offer coverage with some kind of parameters, we could collect the data over time." He offered gastric balloon technology, such as the *Orbera* system from **Apollo Endosurgery Inc.**, as one specific example where the evidence suggested a benefit but wasn't sufficient for coverage. Devices such as gastric balloons, bands and sleeves have gained popularity in treating obesity in recent years. *(Also see "Obesity 2016: Minimally Invasive Bariatric Devices Gaining Steam" - Medtech Insight, 20 Jul, 2016.)*

While some bariatric surgery procedures, including traditional open and laparoscopic Roux-en-Y gastric bypass and laparoscopic adjustable gastric banding, are nationally covered by Medicare. Other procedures, including open sleeve gastrectomy and gastric balloons, are nationally non-covered under current CMS policy.

MEDCAC panels judge the strength of evidence supporting specific therapies, but CMS is not required to follow the committee's recommendations in making coverage decisions.

The panel's recommendations tracked observations made by the Agency for Healthcare Research and Quality in a draft technical assessment released before the meeting. The report noted there are no randomized trials that specifically evaluate the effectiveness and safety of bariatric surgical or endoscopic procedures among Medicare patients, and few overall that compared results from differing bariatric surgery techniques.

However, AHRQ acknowledged that evidence collected in younger patients "strongly suggests that bariatric surgery overall as well as certain procedures are both effective in achieving weight loss and reducing the risk of other non-weight loss outcomes (e.g. sleep apnea, cardiovascular events, etc.) and safe in regards to surgical complications. Nevertheless, evidence from studies in younger populations may not

be directly generalizable to the Medicare eligible population."

Concerns specific to the Medicare population that AHRQ felt weren't adequately addressed included higher comorbidities in older patients, as well as outcomes such as health-related quality of life, hospital readmission after surgery, admission to skilled nursing facilities, and nutritional status.

Patients 65 and older typically haven't been included in weight-loss surgery studies due to a desire for a homogenous study population as well as a now-debunked belief that obesity was less of a problem in older patients, said presenter Shelby Sullivan, who is director of the gastroenterology, metabolic and bariatric program at the University of Colorado. "We now understand that's not the case, but including more Medicare patients could be cost-prohibitive," she said.

Panelists expressed differing views on how well existing data could be matched to Medicare patients.

"We know the Medicare population is more disabled, but not why," said Diana Zuckerman, President, National Center for Health Research. "How do we judge how well they'll do when we know they may be very different from others in their age group?"

However, others on the panel said they felt younger patients could act as surrogates for outcomes in some subgroups, segmented by type of procedure, gender and race or ethnicity.

But while more data on how Medicare patients respond to bariatric surgery is needed, panelists didn't seem to feel it had to come specifically from randomized trials. "We need good-quality observational studies … that control for confounders, modifiers, and so on," said Campos-Outcalt.

The MEDCAC panelists were asked to rate, on a scale of 1-5, how strongly they thought the evidence supported the use of bariatric surgery to treat several conditions, including weight loss, diabetes, musculoskeletal complications and quality of life. All of the ratings comfortably exceeded CMS's threshold (2.5) for coverage consideration, though the panelists expressed less certainty about how successful the surgeries are in creating successful long-term outcomes.

But the ratings collapsed when panelists were specifically asked to rate their confidence "that the predictors of success in the Medicare population (such as patient characteristics and pre- and post-procedure standards of care) for any bariatric therapy is known." The average on that question was just above 2.

"I don't know that I feel confident in what the predictors are, or that I could speak to them intelligently," said panelist Karen Albright, a professor at the University of Alabama at Birmingham. She agreed with fellow panelists that much more predictive work is needed before they would be comfortable recommending full coverage of the surgeries.

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Heading To A Device AdComm? US FDA Details Key Deadlines In Final Guidance

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Medical device developers preparing to bring their products before a US FDA advisory panel should get any briefing materials that include confidential components to FDA about two months before the meeting, the agency said in a new final guidance laying out official standards for advisory panel meetings.

The 17-page document, "Procedures for Meetings of the Medical Devices Advisory Committee," first issued as a draft in April 2015, replaces the 2000 "Guidance on Amended Procedures for Advisory Panel Meetings," as well as the blue book memo "Panel Review of Premarket Approval Applications #P91-2," which was issued in 1991. *(Also see "CDRH Lays Out Inner Workings Of Device Advisory Panels" - Medtech Insight, 31 Mar, 2015.)*

The document recommends that applicants submit both redacted and unredacted versions of briefing materials at least 42 business days before the meeting, with the unredacted version clearly marked as containing confidential information. FDA may then contact the applicant between 42 and 22 days before the meeting to informally discuss "the accuracy, relevance, completeness, and appropriateness of briefing materials and proposed redactions," the guidance document states.

If a briefing packet doesn't include any material that must be redacted, applicants should get it to FDA no later than 22 business days before the meeting. The device center will put the briefing materials online at least two full business days before the panel convenes.

Other recommendations in the guidance discuss slides to be used in presentations during a panel meeting. It asks that any slides containing information that wasn't previously submitted "clearly indicate that the information contained in the slide has not been reviewed by the FDA." In general, FDA recommends applicant presentations and other documents only include materials that have been reviewed by FDA.

The guidance document says FDA may postpone the meeting if developers submit "new data or significant new analyses" between 55 and 22 business days before a panel meeting. And if FDA moves ahead with a scheduled meeting after such new information surfaces, "the affected sections of the Panel Pack should prominently note that such information was not provided to CDRH by the recommended timelines and, as such, has not been reviewed by CDRH," the document states.

Federal law establishes that parties who bring a device to panel "have the same opportunity as the Secretary to participate in meet-

ings of the panel," including addressing the panel to clarify information and calling on experts to address specific issues. In addition, the 21st Century Cures Act specifically required that meetings provide adequate time for initial presentations and "encourage free and open participation by all interested persons." Applicants normally have 60 minutes to present their case for a product, which can be extended to 90 minutes upon request. FDA faces the same time limit for its presentation, the guidance states.

The guidance also notes an add-on requirement from the Cures Act that following the initial presentations, the panel may pose questions to a company's designated representative and "consider the responses to such questions in the panel's review of the device."

Under the guidance, FDA may convene an advisory panel to discuss a premarket approval (PMA), a humanitarian device exemption (HDE) application, or a proposed product development protocol either on its own initiative or at the request of an applicant. "When acting at its own discretion, [the device center] intends to consider taking a matter before a panel if, among other things, the matter is of significant public interest or there is additional or special expertise provided by the panel that could assist the center in its decision-making," the guidance states.

For example, the device center is most likely to ask for panel meetings on PMAs if the device is novel and could have a significant impact on clinical practice; if the study results leave it unclear whether the probable benefits of the device outweigh its probable risks; or if FDA has identified significant problems with the study's data quality or data integrity. The guidance further explains that FDA may call for panel meetings as part of a device classification or reclassification effort, or to seek panelists' expertise on a public safety issue. For example, panels have met in the past to discuss post-market safety issues arising from device failures.

When a panel is discussing a specific device, the panel must include what FDA calls "adequate expertise." Federal statute defines that as a requirement that each panel "include two or more voting members with a specialty or other expertise clinically relevant to the device under review and at least one voting member who is knowledgeable about the technology of the device," the guidance states.

While panel meetings are typically held in person, the guidance allows for meetings to be held by teleconference for "discussion topics that are anticipated to be brief." The teleconferences are usually authorized when a meeting is held to confirm recommendations from an earlier in-person meeting; if time does not permit a meeting to be held; or to speed the classification of multiple lower-risk device types, especially if the devices are no longer widely used, significant scientific evidence exists, or the proposed classification is not expected to be controversial.

The guidance applies only to the 17 industry-specific panels of the Medical Devices Advisory Committee, such as those for circulatory system devices, dental products, and gastroenterology and urology devices. A separate document explains procedures of the Medical Devices Dispute Resolution Panel.

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Standards Conformance Enough To Prove Ultrasonic Therapy Radiation Safety, US FDA Says

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US FDA posted a draft guidance Aug. 30 signaling its plans to accept a declaration on conformity to two International Electrotechnical Commission standards rather than require manufacturers to separately prove compliance to parallel agency regulations for ultrasonic diathermy devices used to address pain relief and related conditions.

FDA acknowledges in the draft guidance that sections of IEC 60601-2-5, "Medical electrical equipment - Part 2-5: Particular requirements for the basic safety and essential performance of ultrasonic physiotherapy equipment," and IEC 61689, "Ultrasonics - Physiotherapy systems - Field specifications and methods of measurement in the frequency range 0.5 MHz to 5 MHz" (2013), adequately address technical concerns that are envisioned by FDA's 21 CFR 1050.10 regulation on radiation safety performance standards for ultrasonic therapy.

As a result, "FDA does not intend to consider whether firms that provide a declaration of conformity and indicate conformance to applicable IEC standards also comply with 21 CFR 1050.10," the draft guidance states.

"Complying with FDA regulations and conforming to the identified IEC standards can cause manufacturers to duplicate their efforts," the agency notes. "FDA acknowledges the advantages of a universal set of device-specific criteria and requirements, and believes that conformance with certain IEC standards would provide at least the same level of protection of the public health and safety from electronic product radiation as the FDA performance standards for ultrasonic therapy products."

The declaration of conformity should be concluded in conduction with a 510(k) submission for qualifying devices. The draft guidance also outlines the key elements that should be included in a 510(k).

The draft explains that the policy targets a specific set of class II ultrasonic diathermy, or physiotherapy, devices that are used to apply therapeutic deep heat for selected medical conditions such as relief of pain, muscle spasms and joint contractures. It does not apply to other devices that use ultrasound to, for example, destroy things like kidney stones or sensitize tissue to support cancer therapies.

Public comments are due on the draft guidance by the end of October under FDA-2017-D-4764.

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