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FDA Looks For Diverse CMMI 'Maturity' Pilot Enrollees; Device-Makers Expect Big Savings

ELIZABETH ORR elizabeth.orr@informa.com

US FDA is looking at ways to enroll a more diverse range of companies in its new Voluntary Medical Device Manufacturing and Product Quality Program, which aims to gauge the manufacturing maturity of device-makers, agency officials said at an Oct. 10 meeting.

Under the pilot, the quality systems and manufacturing processes of participants will be evaluated by third-party appraisers against the Capability Maturity Model Integration (CMMI) appraisal framework. Results of a manufacturer's CMMI assessment will be shared with FDA; the agency will then use the information to help shape its regulatory, compliance and enforcement decisions.

Last year, FDA – along with the Medical Device Innovation Consortium (MDIC) – tested CMMI assessments in a "pre-pilot" program involving three unidentified companies. *(Also see "Quality On The Brain: FDA Maturity Pilot Aims To Shift Industry's Compliance Mentality To A 'Quality Mindset'" - Medtech Insight, 29 Sep, 2017.)* Now the agency wants to roll out a pilot that it hopes will include at least 30 companies and will run from January through December 2018. Manufacturers can enroll now through September 2018, and several companies have already expressed interest, FDA says.

Executives from two of those firms, **Medtronic PLC** and **Edwards Lifesciences Corp.**, spoke at the meeting and said they believed the program would lead to significant savings.

FDA doesn't expect much trouble recruiting larger firms such as those for its upcoming pilot, but it surmises it might have some difficulty finding an adequate number of small and midsize companies to play. Because the agency wants to make sure that the full pilot tests the maturity model at companies of all sizes, it is considering ways to lower costs or alter enrollment criteria so smaller firms can participate.

"Enrollment is site-specific," said Sean Boyd, deputy director of regulatory affairs at the FDA device center's Office of Compliance. "We want to enroll a range of sites, so we may include different paradigms."

Developed in the 1990s by Carnegie Mellon University's Software Engineering Institute in Pittsburgh, and now administered by the CMMI Institute, CMMI is based on the Capability Maturity Model. "Maturity" in the context of manufacturing means that companies

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Philips' Profit To Be Dented By FDA-Decreed AED Sales Halt

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Philips Healthcare will see its bottom-line over the next few quarters suffer the brunt of a US consent decree, under which the company has agreed to suspend production and distribution of automatic external defibrillators manufactured at two facilities in Andover, Massachusetts, and Bothell, Washington.

The decree results from FDA inspections of those facilities conducted between 2009 and 2015. The agency found several counts of non-compliance of current good manufacturing practice requirements. The issues were largely to do with processes and documentation associated with process control and manufacturing, according to a Philips spokesperson.

The Dutch group has already been taking the necessary steps to meet the FDA requirements and has addressed many of the deficiencies the agency cited. While there is still "more work to be done " – for example, in complaint handling, an area which is "a never-ending story" due to the evolving regulations – Philips is "in a much better shape" than it was in 2015," the spokesperson told *Medtech Insight*.

The decree calls for Philips to halt the manufacture and sales of external defibrillators made in the Andover and Bothell facilities until the firm satisfies the FDA's requirements. Philips said it hopes to resume the suspended defibrillator production "in the course of 2018."

Not all the AEDs are affected by the decree; the agreement still allows Philips to continue manufacturing and shipping the line of *HeartStart HS1* AEDs (including *HeartStart Home* and *HeartStart Onsite* AEDs) to meet public health needs. Additionally, Philips can manufacture and ship devices under certain circumstances to customers that rely on *Philips FR3* AED in their standard practice of care and want to order more. The decree also Philips to continue to service Emergency Care & Resuscitation devices and provide consumables and the relevant accessories.

The external defibrillator lines that are affected by the decree contributed around €35m in sales each quarter in 2016. Due to the suspension of the device lines, profit disgorgement payments and costs of preparing for and handling more regulatory inspections to come, Philips expects EBITA in the fourth quarter to be impacted by €20m in the fourth-quarter for 2017, and by €60m in 2018.

The Andover and Bothell facilities also manufacture other products related to the ECR business, such as non-invasive blood pressure cuffs, among other things. The manufacturing of these devices, as well as products from other patient care businesses made at these facilities, will continue as usual, but will be subject to increased scrutiny for compliance.

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have adequately developed practices and processes to ensure that quality is pervasive throughout their organization.

FDA and MDIC, which are working together on the pilot, evaluated 22 quality appraisal system models before settling on CMMI because of its flexibility, record of accomplishment, and direct connections to medical device regulations.

Firms that take part in the pilot will qualify for incentives such as waived pre-approval inspections or leeway on 30-day notice manufacturing-change submissions. *(Also see "Gifts For Industry: From Waived Inspections To Pre-Market Leeway, US FDA Woos Firms For Maturity Pilot" - Medtech Insight, 25 May, 2017.)*

Despite FDA's outreach to smaller and midsize firms, there will still be some gaps in the more representative set of companies chosen for the pilot. For example, there's no clear process for combination products manufacturers to participate. George Zack, a principal at Michigan-based Two Harbors Consulting, said organizations supporting the pilot program have been speaking with FDA's drug center and looking for ways to integrate pharmaceutical standards. Zack is working with the CMMI Institute to manage the pilot.

Further, companies that want to join the pilot must have had a "successful" audit within the past four years. FDA defines "successful" as having been inspected by FDA with a result of "No Action Indicated" (NAI) or "Voluntary Action Indicated" (VAI), or by a Medical Device Single Audit Program (MDSAP) auditor with a result of minor nonconformances.

"We want to allow new, struggling firms to participate eventually, but for now we expect sites with a clean compliance record" to participate, Boyd said.

CMMI's conversations with early adopters have lead it to estimate that pilot-program participation will cost around $25,000 to $35,000, said Kim Kaplan, program operations manager at the CMMI Institute. However, she noted, the group hopes to eventually implement a tiered structure that would allow smaller manufacturers to pay less.

A Federal Register notice recruiting participants will be published in the next several weeks. But agency officials stressed that the pilot is still a work in progress, and is expected to evolve. "We don't know everything yet," said Robin Newman, director of CDRH's Office of Compliance.

"It's OK to go into this not knowing a lot of the answers."

FIRMS FORESEE BIG SAVINGS

Medtronic and Edwards have told FDA they plan to participate in the pilot. Executive from both firms said at the Oct. 10 FDA meeting that they believed CMMI appraisal costs would be offset by savings elsewhere. For example, Nathan Tenzer, director of manufacturing for Edwards Lifesciences, said they expected to save $120,000 in manufacturing submissions costs in the pilot's first year. Edwards is one of the five manufacturers who have signed up to participate in the pilot as an "early adopter."

Tenzer was also enthusiastic about the ability to bypass 30-day notices, a submissions process that sometimes leads to unintended consequences, he said. For example, the company chose to install a back-up water circulation loop after learning that upgrades they wanted to make to the system could put the production line out of commission for 12 weeks, once 30-day submission preparation and review was included. The back-up system cost $66,000, while just doing the upgrade would have cost $1,350.

Luann Pendy, senior VP of global quality for Medtronic, seconded Tenzer's comments about savings. "It's more expensive to have poor quality than good quality," she said. For example, Pendy said one large Medtronic facility could save $1.7m by not having to submit 30-day notices. She also noted that each CAPA – a Corrective and Preventive Action following a product nonconformance – can cost a firm $50,000 to $100,000, and responding to an FDA-483 form following an unfavorable agency inspection can cost anywhere from $500,000 to $1.5m.

FDA was surprised to learn how significant the 30-day notice benefit was to manufacturers, said Francisco Vicenty, a program manager for the joint FDA/Medical Device Innovation Consortium Case for Quality.

Thirty-day notices are intended to support changes to the manufacturing procedure in methods of manufacture that don't alter performance or design specifications, or the designated physical or chemical specifications of the finished device. A firm can implement the change 30 days after submission unless FDA notifies the manufacturer that more data is needed before that time. The process was intended as a simple way to update FDA, Vicenty said, but staff working on the pilot program have learned that the wait often delays innovation and causes unnecessary spending as manufacturers install redundant systems to avoid delays.

The project could help improve patient care and increase public trust in the medical device industry by allowing manufacturers to hone in on metrics that matter most to patients, Medtronic's Pendy said. "I believe the maturity model will allow for faster innovations, and generate a level of trust and transparency that's missing," she said. "When we have it, we can all meet our mission of treating patients."

BOTTLENECK CONCERNS

While most comments were positive, meeting attendees showed some concerns. Some manufacturers expressed apprehension after CMMI's Kaplan mentioned that the institute is selecting appraisers with medical device or regulatory expertise for the pilot from a pool of 380 certified professionals. The pilot team should be fully trained by the end of October, she said.

Some companies at the meeting said they were concerned that the relatively small group of appraisers might lead to a "bottleneck" and long delays as participation in the program grows. Two Harbor's Zack said CMMI has considered that and will ease its standards or allow candidates to apply, rather than recruit, if it becomes necessary.

Another attendee asked whether the group included appraisers who had expertise in all device-industry sectors. In response, Vicenty said participants would be visited by appraisers with expertise in the company's sector as much as possible.

Zack also addressed concerns around proprietary information, emphasizing that CMMI wouldn't share identifiable information without permission. However, he noted, companies can share their results as they see fit, including by discussing it with clients or patients.

"We're hoping to trend the data to show overall strengths, weaknesses and how companies overcome common obstacles," Zack said. "And then manufacturers can share it back to show how they're creating quality."

FDA will collect comments on the program via the reopened regulatory docket through December 2017, and via the CaseForQuality@fda.hhs.gov email address throughout the pilot.

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What Happens After Joining?

After a device manufacturer applies online to participate in the Voluntary Medical Device Manufacturing and Product Quality Program:

- **Within five days:** FDA decides whether to enroll the company.
- **Within 30 days:** The company, FDA, MDIC and the CMMI appraisal team plan and schedule the appraisal.
- **Within 90 days:** CMMI appraisers visit the facility and appraise critical areas, then pass along their findings to FDA.
- **Ninety to 180 days post-appraisal:** FDA, MDIC, the firm and the CMMI Institute follow up to review the appraisal results and plan any required additional review. The company should begin seeing earned benefits from FDA, such as their removal from FDA's work plan for routine facility inspections.
- **One year post-appraisal:** The company undergoes another appraisal tailored to meet any updated needs.
- **Ongoing:** The CMMI Institute collects appraisal data for trending and reporting.

Contradictory Messages Over Medtech and Brexit: MDR? No MDR?

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There is no certainty over the future of UK medtech after the Brexit process is complete. As a result, many UK regulatory stakeholders in the sector feel the need to take contingency action now to insure against the worst-case scenario -- no agreement with the EU on medtech regulations.

Indeed, the messages circulating about possible post-Brexit plans for medtech regulations in the UK are confusing and contradictory, as delegates found at recent meetings in London.

The topic was high on the agenda at an Oct. 3-4 conference convened by The Organisation for Professionals in Regulatory Affairs (TOPRA) and at a separate event on October 5, run by the Association of British Healthcare Industries (ABHI).

An increasing number of stakeholders suggest they have no choice but to move before it's too late. Notified bodies, authorized representatives and device companies are taking measures, including voting with their feet. Even the UK healthcare products authority, the MHRA, is basing some decisions on a future in which it may no longer be part of the EU.

The new EU Medical Device and IVD Regulations entered into force in May 25, and preparations for new structures under the regulations are underway. As a result, many feel they need to establish a base outside of the UK to ensure they are part of the EU regulatory machinery - in which their history lies - that will continue after March 30, 2019. Otherwise, stakeholders fear they may risk entering regulatory oblivion.

Offices and headquarters are already being created abroad. John Adcock, managing director of authorized representative Advena told *Medtech Insight* at the ABHI meeting about his company's new office in Malta, while Brussels is where the European Association of Authorized Representatives has created a new site. Meanwhile, the large notified body BSI has opened a second EU notified body office in the Netherlands (building on an existing national office there) and has formally applied for designation under the medical device directives within the oversight of the Dutch Health Inspectorate (IGZ).

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"Brexit negotiator's timelines don't match industry's ... It is very difficult to prepare for the unknown," says Virginia Acha, Association of the British Pharmaceutical Industry.

If there was more certainty, such moves may not be considered necessary.

Nick Baker, head of UK LRQA, a notified body for medical devices, told the TOPRA meeting that, even though his organization supports the so-called "preferred option" - the UK applying the new EU regulations post-Brexit - UK LRQA has decided it needs to relocate its main office. Notified bodies are in the same boat as the device industry, he said, and have a "no-go" date beyond which they cannot wait any longer for a decision over what will happen to medtech regulations post-Brexit.

Virginia Acha, executive director, research, medical and innovation at the Association of the British Pharmaceutical Industry (ABPI) echoed these sentiments at TOPRA for the broader life sciences industry: "Brexit negotiator's timelines don't match industry's … It is very difficult to prepare for the unknown," she said.

DATES CONSPIRE AGAINST UK APPLYING MDR/IVDR

So why is there so much uncertainty? It all relates to the timing of the full application of the Medical Devices and IVD Regulations, and a delay that was granted on behalf of the UK government, which recognized that the medtech sector is in a particularly difficult position.

Since the date of application of the MDR is May 26, 2020, and the date of application

of the IVDR is May 26, 2022, the new regulations will still be in the middle of a transition period at the time the UK leaves the EU.

During her speech on September 22 in Florence, Italy, UK Prime Minister Theresa May made it clear that the UK's EU Withdrawal Bill will ensure that EU rules and regulations are carried over into domestic law the moment the UK leaves the EU – on March 30, 2019.

In other words, as John Wilkinson, head of devices at the UK's MHRA, acknowledged during the first day of the TOPRA meeting, the EU legislation is cut and pasted into UK Regulation as of that date.

"But," he said, the medical device legislation is "overwhelmingly more complex than anything else on the statute books and will remain so."

The reason for this is that direct EU legislation is only converted and incorporated into domestic law if it is operative immediately before exit day. If the date of application of a regulation falls after exit day, then the provision is not converted. Because the EU's new Medical Device and IVD Regulations will only be part-way through transitioning into EU law in 2019, it implies that these regulations will not apply in UK law post-Brexit.

Moreover, given that a significant proportion of the 80 delegated and implementing acts underpinning crucial elements of the MDR and IVDR will not be introduced until well after exit day – and potentially not for many years afterwards – the EU would be continuing to shape UK regulation well after exit day. And that is something that the UK government is unlikely to accept, experts explained at the recent meetings.

TWIST IN THE TALE

But there is a question mark over this interpretation. Neil R. Armstrong, CEO of the MeddiQuest Regulatory Affairs consultancy, which has also set up offices in Ireland, pointed out that Parliamentary Under Secretary of State for Health Lord James O'Shaughnessy, gave a speech at the annual ABHI Market Conference on September 14 (just before May's speech in Florence), in which rallied for what the UK medtech sector considers the "preferred option."

> "We would absolutely support a UK that remains actively engaged in the MDR and IVDR," says MedTech Europe's Oliver Bisazza.

During that speech, O'Shaughnessy acknowledged that the UK, and the EU, would cope in the case of a "no deal" scenario – by this he was referring to the UK government failing to make any agreement with the EU and simply having to walk away. There are fears this is becoming more possible, with Prime Minister May admitting on October 10 that she expects the stalemate to continue for another year.

But O'Shaughnessy pointed out: "Elements of the new regulations have been applied directly in UK law since May, meaning devices can now be legally placed on the UK market if they are in conformity with the new regulations, invoking all relevant requirements. As it stands, the EU (Withdrawal) Bill would maintain this position beyond March 2019".

So where does medtech stand? If Shaughnessy's best-case scenario is correct, all is well and good and the sector can breathe a sigh of relief. But if not, there are two possible ways forward that would retain the preferred option where the MDR and IVDR apply in UK law. One possibility is the UK signs some sort of agreement with the EU that allows this (e.g., a mutual recognition agreement). Another option is that the UK makes a special provision around medtech regulations, or around life sciences in general.

UK GOVERNMENT INQUIRY INTO MEDTECH

As part of the consideration of possible special provisions in the life sciences area, the UK House of Commons select committee on health has initiated an inquiry into the effects of future regulatory systems on medical technology and other health-care products in the UK after the country has left the EU. The inquiry will be followed by only a matter of weeks with public hearings.

The aim of the inquiry is to gather information on the best ways to guarantee a safe and effective supply of medicines, medical devices, medical products and substances of human origin in the UK. The committee is focused on providing certainty and a smooth transition for patients, the UK's NHS and the country's life science industry to the post-Brexit regulatory arrangements.

But for some, this effort has come too late, as the stories of office relocations demonstrate. Others say they urgently need clarification as soon as possible - or "yesterday," as many said at the meetings - to make decisions that will dictate their future strategies.

THE EFTA/MRAS SOLUTION, OR NOT?

During both meetings, much hope was pinned on the UK completing an agreement that would enable the medtech regulatory status quo to continue. There were frequent references to Switzerland, Turkey and Australia and how they have adopted EU legislation, including the medical device directives, through mutual recognition agreements (MRAs) with the EU.

These examples were mentioned by Erik Hansson of the European Commission's Directorate General Grow (Industry). He also noted that the European Free Trade Agreement countries have an agreement with the EU as part of the joint European Economic Area - these countries also take on EU regulations, including the medical device directives.

This raises the possibility of the UK striking up an MRA with the EU, or becoming part of the European Economic Area.

But Armstrong was quick to point out that the prime minister had said in Florence last month that EEA membership would mean the UK having to adopt "at home - automatically and in their entirety – new EU rules." The UK would have "little influence and no vote" over the rules, she warned, adding that "such a loss of democratic control could not work for the British people."

She also discounted the possibility of a traditional Free Trade Agreement of the

type the EU recently negotiated with Canada, *Medtech Insight* notes.

"We can do so much better than this," May said in Florence, adding that the UK government shares "a commitment to high regulatory standards … and to not only protecting high standards but strengthening them."

But beyond that, and May's talk of being "creative" and "practical," it is not at all clear where the UK is heading when it comes to the regulatory aspects of trade.

AN EU PROBLEM NEEDING AN EU SOLUTION

ABPI's Acha reminded the TOPRA meeting that "Brexit is not a British problem, it's an EU problem." These sentiments were echoed by Oliver Bisazza, director of regulations and industrial policy at MedTech Europe, when addressing the ABHI meeting.

Bisazza told ABHI: "We would absolutely support a UK that remains actively engaged in the MDR and IVDR." He referred to the joint UK/EU associations' letter to the Brexit negotiators, calling for the UK to continue in its current path, moving toward the same regulatory future under the Medical Device and IVD Regulations as the rest of the EU, for the sake, among other things, of patient safety, innovation and growth in the industry.

"Both sides would be poorer off the more disengaged we are," he said.

Bisazza called for the UK to not only remain actively engaged in the EU's regulatory system, but also to continue active engagement in the new Medical Devices Coordination Group, which will play a key role in supervising notified bodies and in the governance and implementation of the new regulations.

The MedTech Europe official also acknowledged the contribution that the UK has made to the new regulations implementation task force within the Competent Authorities for Medical Devices group, which it has led.

This task force is about to present a final implementation work plan for the regulations, and then the UK will formally step down as the lead, allowing the remaining members to transition to a possible future without input from the UK at such a level.

But Bisazza, who welcomes the UK's pragmatism in EU matters, made it clear that EU industry wants to see the UK continue its engagement "ideally as a formal member, but in whatever way possible" of both these groups.

CAPACITY AND COMMUNICATION

Bisazza also called on UK notified bodies and other economic operators, including authorized representatives, to be able retain their European status under the new regulations post-Brexit, especially given the significant UK contribution in both these areas.

Ongoing concerns over notified body capacity and availability are challenging enough. Brexit could exacerbate current concerns, he said, wondering what route might be available for the UK notified bodies to continue to audit to EU requirements without moving to another member state.

The UK, for its part, is carrying on as if it is business as usual and delegates learned that the MHRA is supporting applications from UK notified bodies. Nonetheless, experts at the TOPRA meeting said, UK notified bodies are likely to try to establish bases in other EU countries to be sure their assessments are carried out by the authorities of a country that will remain in the EU.

The European Commission's Hansson highlighted during the TOPRA meeting how UK notified bodies and authorized representative play a very important role not only in terms of the services they provide to UK manufacturers but also to non-UK manufacturers, including those from third countries.

Bisazza argued that many authorized representatives will not find it commercially attractive to move out of the UK, especially given the increased product liability and exposure they face under the new Medical Device and IVD Regulations.

It would also minimize disruption for smaller manufacturers, he suggested, if they could remain in the UK and retain their EU status.

And then there is the UK contribution to and benefit of being part of the Eudamed medical device database. If the UK leaves the EU, will all the information have to be entered separately in the UK for registration, Unique Device Identifiers, summaries of safety and performance and vigilance? And what will happen for multi-country clinical investigations, and to data sharing and analysis? There is a great deal at stake.

"The UK's continued contribution stands to reason," Bisazza concluded.

THE EMA TOO

There is also another factor that is significant for the medtech arena, particularly with regards to the future regulation of drug/device combinations – that is, the European Medicines Agency (EMA).

The EMA, too, is well advanced in its Brexit planning. It has been working on a

A Massive Loss To The EU

In his speech on September 14, Lord O'Shaughnessy summarized the UK contribution in terms of notified bodies and authorized representatives:

"Any loss in capacity of third-party assessments, at a time when the new EU regulations will significantly increase demand, is not to be under-estimated.

The five UK notified bodies assess a disproportionate number of medical devices. According to a recent independent assessment of the market, UK notified bodies make up the first, third and fourth largest share of assessors, with the British Standards Institution alone having a remarkable 30% share of the European market. Furthermore, we estimate UK notified bodies oversee between 50% and 60% of all the highest risk devices on the EU market.

We also host over 50% of the EU's authorized representatives for manufacturers based in third countries."

business continuity plan as it prepares to move out of the UK to another European city, and to redistribute product assessment work from the UK to other member states, EMA's Melanie Carr said at TOPRA's medtech meeting. Carr is head of Corporate Stakeholders and interim head of the Stakeholders and Communication Division at EMA.

She talked about the challenges of choosing the new location for EMA while also encouraging staff to remain with the agency. "If we lose over 50% of our staff, we can no longer function," Carr said.

The EMA is also asking industry to prepare in advance of Brexit for the moves and changes. In particular, companies that make drug/device combinations where the drug element is approved by the UK MHRA could face a tough time ahead, with questions about whether assessments performed in UK be valid once the UK is not in the EU.

ONE BIG MUDDLE

Few could have predicted the extent of this impasse and the impact it is having on the UK, and on the EU too.

As MeddiQuest's Armstrong said at the TOPRA conference: "Brexit just complicates everything," coming on top of the "biggest change we have ever had in the EU [in terms of medtech regulations], bigger even that the introduction of the original directives."

And the hope for a solution that is centered around the needs of the medtech industry and patients is, quite frankly, slim. Hansson of DG Grow hit the nail on the head when he pointed out that, as medical devices are not the main concern for the Brexit decision-makers, the outcome for medtech will depend on the nature of the overall agreement.

Looking at the contribution that the UK's MHRA has made to the EU in helping draft the original medical device directives and new medical device regulations, and in all the implementation efforts it has engaged in, the is EU at risk of losing one of its very best medtech regulatory players.

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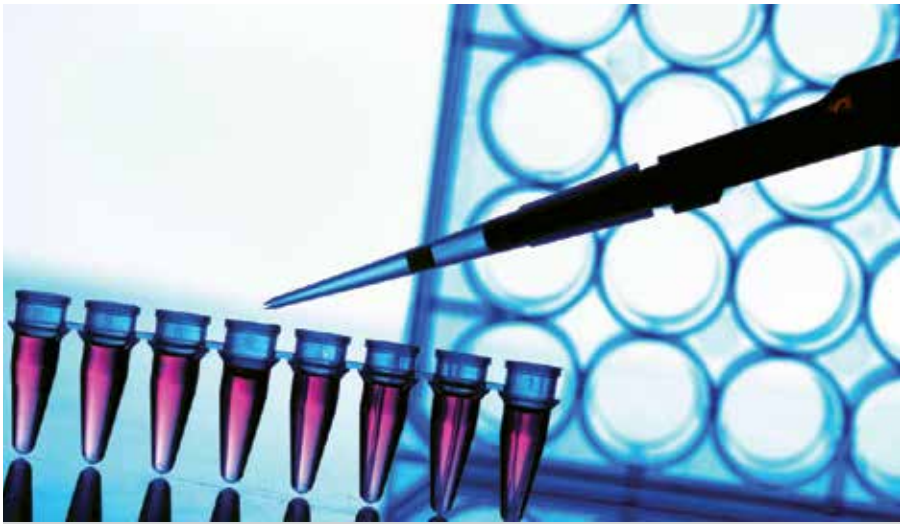

UK IVD Industry Finds New Voice And Appetite For Challenges Ahead

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Some differences are noticeable at BIVDA, the UK IVD association that represents 113 full and 38 associate members serving the UK NHS and private sector, and overseas markets. More broadly, it is the forum for the wider pathology industry across the UK, which in 2016 was a market worth £816m ($1.08bn), with exports adding a further £1.1bn (2013 figure).

Among the new things is a document on *The Value of IVDs*, an eight-page white paper launched this week at the 2017 AGM of BIVDA. The document aims to show clearly the value that the IVD industry brings to the NHS and the wider UK economy. It is a "one voice, one key message" initiative that **Johnson & Johnson Medical Ltd.**'s Patrick Oliver says is a powerful statement about the UK IVD value proposition.

Comments from the floor conveyed approval of what some see as an overdue initiative. Oliver, chair of BIVDA's external affairs working group, told *Medtech Insight* that the effort would be successful if NHS England's decision-makers take on board the points made in the document. Almost equally important is reaching out to politicians and MPs and other stakeholders. The next working group meeting, on Oct. 26, will be an opportunity to take the plans further forward. Oliver is inviting participation and input from across the industry.

Association chief executive Doris-Ann Williams, whose secretariat is finally back up to full strength with the appointment of Chief Operating Officer Sarah Mouzouris, added that BIVDA has begun joint work with AdvaMed and IVD Australia on defining and delivering value.

As to UK affairs, Williams was evidently pleased to report that the four Diagnostic Evidence Co-operatives (DECs) have been re-authorized, albeit under a different name and in a joint concept with devices. The 11 National Institute for Health Research Medtech and In vitro diagnostic Co-operatives (MICs) will receive £14.25m funding over five years and will launch in January 2018.

'THE IVD TECHNOLOGIES INDUSTRY BODY'

BIVDA itself has also undergone a rebranding of sorts and is now describing itself as "the IVD technologies industry body," and using a new mission statement, "IVDs: transforming patient pathways." *(Also see "UK NICE's MedTech Scan Will Give NHS Early View Of Innova-*

tion" - Medtech Insight, 11 Oct, 2017.) The updates are intended to reflect that the organization's field of vision is extending ever more toward point of care, genomics and companion diagnostics, and adds to a sense of change and renewed purpose at the association.

The rebrand was described by BIVDA chairman Simon Richards (**Alere Inc.**) as a fitting way to both mark BIVDA's 25 years industry service and prepare for the next 25. *(Also see "IVD UK Spring Meeting: The Costly But Necessary Route To IVDR Compliance" - Medtech Insight, 26 May, 2017.)* A sound platform will be vital: With the current business environment, NHS and political arena throwing up ever more challenges, Richards believes there could be a "totally unstable environment" if matters are not handled with care.

He sees the priority areas, pinch-points and potential game changers as:

- The Accelerated Access Review (AAR): the UK government should be implementing the AAR over the coming months, but its response to the final report is still awaited. What happens next, and will it do anything to cut the UK's average adoption time for an innovative IVD test from the current 10 years?
- Translating the UK Life Sciences Strategy and NHS Five-Year Forward View into practice, and understanding NHS Improvement's "diagnostics consolidation" program, which has identified 29 potential pathology networks in England to deliver efficient, high-value pathology services – each network will have a *hub laboratory* for non-urgent tasks, and *spokes* (Essential Services Laboratories) for the essential tasks;
- Brexit, which is already slowing UK GDP while consumer debt is rising. What does this mean for NHS funding? Meanwhile, BIVDA wants the UK to align with the EU IVDR, and retain notified body and competent authority status to allow mutual acceptance of IVDs;
- The pace of regulation, which is speeding up, while the regulations themselves become more complex. Included in this is conforming to the Code of Conduct and the employee credentialing program;
- Precision medicine, where the value of IVDs is being recognized, but the challenges nevertheless remain;
- Integrating the digital agenda and broaching thorny issues such as "who owns the data?"
- How to agree and manage tenders, and handle post-tender challenges; and
- Social norms, which are changing; the crisis in social care funding and delivery; and the trend for individuals, generally, to expect more from the NHS.

But in some of these challenges also lie opportunities. Delegates at what will be BIVDA's last autumn AGM – from next year it is moved back to the spring – went away knowing the size of the task ahead. The mood is far from one of despair, but of pragmatism and a readiness to deal with the issues that have been put in front of the industry – however much it may oppose some of them.

In this vein, a more inclusive BIVDA is working on a new strategy for new times. It has issued a survey to members about how it should focus its activities and meet industry's needs better.

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Medtech Fees To Soar In Canada Under Government Proposals

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The fee Health Canada charges companies to review marketing applications for Class III medical devices could be set to soar from CAN$5,691 to CAN$13,861, according to the government department, which is proposing to hike its fees for regulatory activities across the board for medtech and pharma products.

License evaluation fees could rise from CAN$9,687 to CAN$32,267 for Class III near-patient *in vitro* diagnostic devices, and from CAN$12,347-22,560 to CAN$30,063 for Class IV devices, according to the proposals, which Health Canada has issued for consultation.

"The fees, as they stand now, do not reflect the current costs of the department," Health Canada said. The fees for devices and human drugs were last updated in 2011 based on 2007 costing data, the agency says.

Health Canada said it faces an increasing volume of work on top of added complexity from globalization, technological advancement and more sophisticated data and systems. "These factors have increased the costs of doing business, and placed

pressure on the ability of the Department to deliver services with existing resources," it explained, adding that taxpayers were "assuming an increasing economic burden because of outdated fees charged to industry."

Stakeholders are invited to provide their feedback on the consultation by Jan. 4, 2018.

The proposed fees are set at 90%-100% of the costs to Health Canada, compared with the current fee-setting ratio that is based on 50%-100%. Fees are currently adjusted upward 2% annually. The government department wants to replace this with an annual fee adjustment tied to the consumer price index (CPI) from the prior year.

Fee updates at present are irregular and unpredictable, Health Canada says. Under the proposals, they would be reviewed annually and adjusted accordingly; this includes decreases and increases.

Regarding medical device evaluations, most existing fee categories would remain unchanged. Exceptions here relate to fee categories for Class IV medical device applications for near-patient *in vitro* diagnostics or for devices that contain human or animal tissue – these applications would be processed under the Class IV medical device application category (i.e., merged into a single category), Health Canada said. In another exception, new fee categories would be introduced for Class II license amendments (CAN$320) and private label applications and amendments (CAN$172).

ESTABLISHMENT FEES TO GO DOWN

The consultation document also sets out new fees for Class II device licence reviews (up from CAN$397 to CAN$627) and reviews for Class III device changes-in-manufacturing submissions (up from CAN$1,433 to CAN$9,956). In addition, it addresses fees for post-marketing activities (i.e., the medical device "right to sell" fee) –the annual fee for the right to maintain a medical device on the Canadian market would rise from CAN$375 to CAN$500.

Fees would be "reviewed annually and adjusted accordingly; this includes decreases and increases," Health Canada says.

Medical device establishment licence fees, on the other hand, would go down – from CAN$8,109 to CAN$4,500 – "to reflect updated costs."

Regarding fee mitigation, new companies meeting the Treasury Board Secretariat's definition of a small business would be eligible to receive their first pre-market submission free if the fee is greater than CAN$10,000, one time only, the proposals state. There would also be a waiver for submission-evaluation fees for certain products that address urgent public health needs. The current fee-deferral mechanism would be eliminated.

Medical device license application fees would have to be paid in full before review/processing can began.

All of Health Canada's existing performance standards for medical devices would remain unchanged. The consultation document proposes that "all individual applications/licenses/decisions that are not completed within the established performance standard would be rebated 25% of the fee." This method is only feasible with the inclusion of a stop-the-clock provision, which pauses the performance-standard count in defined circumstances, Health Canada says.

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Patients Want Industry To Minimize Burdens, Augment Comforts Of Device Trial Participation

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At the first meeting of the FDA device center's Patient Engagement Advisory Committee meeting, patients and advocacy groups ticked off a list of perceived barriers to more patient engagement in medtech product clinical trials, including patients lacking knowledge on availability of trials, burdens of getting to the trial site, losing work time, and being kept in the dark about trial outcomes while taking part.

The goal of the first meeting of the PEAC, held Oct. 11-12, was to examine how sponsors and FDA can help design clinical trials with patient input in mind. *(Also see "US FDA's Device-Focused Patient Engagement AdComm Tackles Trial Challenges" - Medtech Insight, 25 Jul, 2017.)* That includes learning about barriers cited by patients challenging their ability to enroll in trials, maintain participation in them and learne about trial outcomes, said CDRH acting assistant director of strategic programs, Michelle Tarver, summarizing the meeting's first day outcomes.

Meanwhile, industry participants at the Gaithersburg, Md., advisory panel meeting expressed concerns that there might be legal and regulatory barriers to trial participation by some patients, that the quality of data could be impacted by increasing patient input, and about the potential loss of confidential business information.

To minimize trial burdens on patients, while augmenting their "comforts," participants at the meeting suggested sponsors reim-

burse participating patients for their travel costs and food costs near a trial site, or even pay for those who could not arrange for paid annual leave from their employer when they take a day off for trial participation.

Also, trial sponsors might consider maximizing the use of electronic devices for recording patient outcome measures to reduce the time patients must spend at clinics or cut down on the frequency of clinic visits.

Some of the roundtable participants also mentioned "the importance of small courtesies – the need for more 'thank-yous' and for clinic staff being pleasant to trial participants, or for sponsors to have continuing conversations with patients so they know what's going on," Tarver summarized. Such steps would go a long way toward making patients feel more like trial participants, rather than a group of people who were having something "just done to them," she remarked.

Also, underscored Tarver, "Every single table I listened to mentioned the importance of closure, because the patients had given a significant amount of time to participation in the trial, they'd given a lot of their resources, so they wanted to know it was beneficial, and added to our scientific knowledge."

PATIENT INPUT WILL DRIVE MORE PRODUCT 'GO' DECISIONS

Despite these barriers, FDA is committed to basing more of its product review decisions on patients' preferences regarding the risks and benefits of devices, FDA Commissioner Scott Gottlieb said, addressing the meeting Oct. 11.

"Involving the end-user – the patient – in identifying health priorities and outcomes desired from health interventions is critically important. This requires … processes that ensure routine integration of these patient perspectives at each key stage of product development," Gottlieb noted.

CDRH Director Jeff Shuren highlighted one obesity device based on patient preferences. That was **EnteroMedics Inc.**'s *Maestro* rechargeable system, a pacemaker-like device used to help obese patients control hunger cravings, approved early in January 2015. *(Also see "FDA Weighs Patients' Risk Tolerance in Approving Obesity Device" - Medtech Insight, 14 Jan, 2015.)* While the device failed to meet its co-primary efficacy endpoints in a pivotal study, the agency took into consideration patients' willingness to accept the higher potential risk of the device, in the approval decision.

The device center has also considered patient input in clearing home-use dialysis equipment, and to improve the design of a glucose monitoring device, Shuren said, cautioning, "It's not about just getting timely access to new technology on the market; it's also about protecting patient health."

GETTING PATIENTS INVOLVED IN TRIALS

Because patients have a hard time simply learning about clinical trials that might assist in their care, more effort needs to go into getting surgeons who implant devices, as well as general practitioners, who generally have more interaction with patients, to get the word out to patients about new trials, participants at the meeting said.

Websites including "Patients Like Me" are good resources for patients to get more information about ongoing trials in specific disease areas, suggested Faye O'Brien, outsourcing program director at AstraZeneca. The US HHS-run ClinicalTrials.gov was also cited as a resource, but some panelists said the site was too difficult for the average person to navigate.

Participants at the meeting, after breaking out into small groups for discussions on clinical trial recruitment, also presented some solutions for overcoming recruitment and retainment barriers.

One suggestion was to involve more patient advocacy groups in the efforts, because they have access to rich patient networks that could be very useful for trial designs.

However, some industry members participating in the roundtables said certain patient advocacy groups could have biases that might impact trial-design components. Others raised concerns, in particular, that some patient advocacy groups are skewed toward one demographic or another, and therefore may not represent all patients with a particular disease or condition.

GETTING PATIENTS ENGAGED IN TRIAL-DESIGN CONVERSATION

Because not all patients are up to speed on medical terminology, an effort must be made to educate potential trial participants in what to expect from the trial, and the companies' motivations for running a study. For example, there needs to be fluency in language, between the patients, the providers, companies and the protocol designers, noted FDA staff recording patients' responses at the meeting.

Some roundtable participants suggested more communication during the protocol design phase between sponsors and trial participants, and not just during presentation of informed-consent documents.

Also, "we need to present data in a way that is understandable to patients, so they feel empowered with that information," said panel member Cynthia Chauhan, who has also served as an FDA patient representative for the National Mammography Quality Assurance Advisory Committee.

PATIENT ENGAGEMENT TEAM

"FDA will take additional agency-wide steps in the coming months to build on these and other efforts," said Gottlieb. "One of those is the creation of a new team that will be responsible for the coordination of certain agency-wide and multi-center projects related to patient engagement."

The team would work to establish consistent approaches to building assessment tools, such as patient-reported outcomes measures, and maintain robust data-management systems to help share knowledge provided by patients and communities, Gottlieb added.

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Device Designed To Improve Spine-Surgery Outcomes Gets FDA Panel Date

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Intrinsic Therapeutics Inc. says a 554-patient randomized, superiority trial supports use of its *Barricaid* device following a standard spine procedure to prevent re-herniation and recurrence of pain or dysfunction. In December, a US FDA advisory panel will weigh the evidence.

The agency issued a notice Oct. 16 announcing that its Orthopaedic and Rehabilitation Devices Panel will meet Dec. 12 to consider Intrinsic's PMA for the Barricaid anular closure device. The meeting will come about one year after the firm completed its PMA submission for the device, including two-year outcomes from the 554 patients. The firm has yet to release the data from that trial, but it says that the study is the first superiority trial for a device of this type.

The Barricaid is designed to close the hole that is left in a disc's anulus (outer ring) following a discectomy performed to treat back pain. Evidence suggests that the opening increases the risk of re-herniation and re-operation, and while surgeons' efforts to remove most of the material inside the disc helps obviate that risk, this action can increase chronic pain. Adding Barricaid to the discectomy procedure can help address this conundrum, the company suggests. The study specifically enrolled patients deemed to be at greatest risk of re-herniation and reoperation.

The Boston-based startup announced a $49m financing round in May including funds from New Enterprise Associates, Delos Capital and CRG. "The company has generated conclusive clinical data which supports a large global opportunity including the US market as early as next year," said investor Jeani Delagardelle in May, when she joined Intrinsic's board to represent Delos.

Intrinsic is specifically seeking an indication in patients "with radiculopathy (with or without back pain), a posterior or posterolateral herniation, characterized by radiographic confirmation of neural compression using magnetic resonance imaging, and a large anular defect (e.g., between 4-6 mm tall and between 6-12 mm wide) post discectomy, at one level between L4 and S1."

The panel meeting will be held in Gaithersburg, Md.

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New Connected-Health Standards Signal US FDA's Future Thinking

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US FDA newly recognized multiple software and informatics standards this summer, including seven dealing with "personal health device communication" for different types of equipment. The move signals an expectation by the agency that it is going to receive an uptick in submission in this area, stakeholders say.

The notice issued by the agency in August recognized standards (contain in versions of the ISO/IEEE 11073 standard) for personal health devices including those used for glucose meters, as well as for continuous glucose monitors, electrocardiographs, insulin pumps, urine analyzer and sleep-apnea and respiratory equipment.

Anura Fernando, principal engineer for medical systems interoperability and security at the standards organization UL, says new technology tend to face additional regulatory burdens trying to get to market, but recognizing these standards helps facilitate a smoother pathway to market.

WIRELESS COMMUNICATIONS STANDARDS

Wireless communication capability is one area that UL and others says will be crucial to the development of new medical devices. As a result, UL and other standards groups engaged with FDA and other government agencies, such as the Office of the National Coordinator for Health IT, to talk about what standards would achieve the right balance of regulatory oversight potential risks.

Michael Kirwan, VP of Continua at the Personal Connected Health Alliance, was instrumental in getting FDA to recognize several of the standards in the notice, especially the ISO/IEEE 11073 communication standards. That effort has been going on for more than 11 years, starting when Continua, an alliance of health-care stakeholders focused on connected health, started developing their design guidelines. *(Also see "Tech Alliance Seeks Standardized Framework For Electronic Device Network" - Medtech Insight, 12 Jun, 2006.)*

He says the standards group's vision is to develop plug-and-play standards for remote patient monitoring outside of the hospital setting. About a decade ago, h the alliance brought together members to come up with the standards that FDA is now formally recognizing.

"At the time, there wasn't anything like it and today you can even argue that the divi-

sion of Continua Health Alliance was fairly broad, probably too broad, that it almost killed it," said Kirwan. "It has been revived now through what is now the Personal Connected Health Alliance, which is a strategic business unit within [the Healthcare Information and Management Systems Society]."

"Our members who go through FDA certification or regulatory clearance in any country have actually asked and pushed, 'Hey we use these standards…we trust it and it's certified by Continua," he added.

SPEEDING APPLICATION APPROVALS

Part of the argument made by PCHA/ Continua' members for recognizing the standards is that it will help speed medical device clearances, Kirwan says. FDA reviewers already know and understand the standards and the tools that validate them, and, over the years, the group has met with FDA officials such as Bakul Patel, associate director for digital health at CDRH, to get them recognized.

"The fact that the FDA recognizes these standards...for the medical device industry this is a signal that this will speed up your 510(k) clearance," he added.

Kirwan says the standards mean FDA can be confident in the scope of the device's data communication and terminology used by the sponsor. On the other hand, proprietary devices that don't use those standards and go through FDA clearance would have to go provide additional information to convince the agency that the device meets its requirements.

A major component of the newly recognized standards is the methods they outline to show that time stamps used in transmitting data are reliable, and Continua has developed software libraries and codes to ensure that. On top of that, the standards include protocols for localization and time zones that ensure confidence of in vital-signs data monitored by patients and clinicians.

THINKING AHEAD ON DISEASES

UL's Fernando said the standards groups and FDA have also discussed what products are likely to come to market with connectivity and communication features. One area identified as a priority is diabetes, which is why standards for glucose meters, continuous glucose monitors, and insulin pumps have been recognized.

"Diabetes is one of the biggest health problems in the United States...when the FDA recognizes these standards, that's a signal to the industry what the FDA is interested in looking at," said Fernando.

For clinical areas like diabetes and aging, and trending areas of technology in medicine such as nanotechnology, standards are needed that allow efficient and reliable use of "big data" to help solve societal problems, Fernando explained.

"When these kinds of standards are developed, there are big sociotechnical megatrends," said Fernando. "What I mean by that is that society is encountering some kind of a problem or issue and then the market, the manufacturers, are trying to address that issue, often using technology." When FDA recognizes new standards it facilitates that process, he says.

The standards, developed through consensus by a broad coalition of stakeholders, send signals to everyone else on what issues new technology should try to address.

"From a very general perspective, what this kind of information does is it allows for innovation not only from established manufacturers in that space but also from those who are associated with that space for example mobile apps," Fernando added.

CYBERSECURITY AND INTEROPERABILITY

The fundamental issue for developing health communication technologies is figuring out whether there is data integrity between the transmitting device and the receiving device. Merging traditional medical devices with mobile apps, relying on these recognized standards, has huge potential to change health care, but, Fernando notes, cybersecurity standards are a crucial element.

Newly Recognized Standards

- **ISO/IEEE 11073–10406 First edition 2012–12–01:** Health informatics—Personal health device communication—Part 10406: Device specialization—Basic electrocardiograph (ECG) (1- to 3-lead ECG).
- **IEEE 11073–10417–2015:** Health Informatics—Personal Health Device Communication, Part 10417: Device Specialization—Glucose Meter.
- **ISO/IEEE 11073–10419 First edition 2016–06–15:** Health informatics—Personal health device communication—Part 10419: Device specialization—Insulin pump.
- **ISO/IEEE 11073–10421 First edition 2012–11–01:** Health informatics—Personal health device communication—Part 10421: Device specialization—Peak expiratory flow monitor (peak flow).
- **IEEE 11073–10422–2016:** Health informatics—Personal health device communication, Part 10422: Device Specialization—Urine Analyzer.
- **ISO/IEEE 11073–10424 First edition 2016–06–15:** Health informatics—Personal health device communication—Part 10424: Device specialization—Sleep Apnea Breathing Therapy Equipment (SABTE).
- **ISO/IEEE 11073–10425 First edition 2016–06–15:** Health informatics—Personal health device communication—Part 10425: Device specialization—Continuous glucose monitor (CGM).
- **UL 2900–1 Ed.1 2017:** Standard for Software Cybersecurity Network-Connectable Products, Part 1: General Requirements.
- **IEC 82304–1 Edition 1.0 2016–10:** Health software—Part 1: General requirements for product safety.

Also included in the recent list of newly recognized standards is UL 2900–1 Ed.1 2017: Standard for Software Cybersecurity Network-Connectable Products, Part 1: General Requirements.

"Cybersecurity standards can let manufacturers take their product to FDA and say, 'Here's what I've done to do my due diligence to have these products tested, so please use this to have confidence I've done what I needed to do,'" said Fernando.

Over the past few years there's been an increasing concern with potential vulnerabilities on connected medical devices that could allow hackers to steal patient data, implant malware or even harm patients. Fernando says cybersecurity standards are also integral to FDA's push for more interoperability between devices and electronic health records.

"These give manufactures a good set of tools [to show] whether or not the products they are developing will satisfy FDA," he added. "These are complimentary to FDA guidances."

NEXT UP: MORE STANDARDS AND PRE-CERT PROGRAM

According to Kirwan, Continua has more standards that it would like FDA to recognize. To date, he says they have issued 18 medical device protocols, of which about a dozen have been recognized by the agency. Currently they are working on getting standards recognized that include protocols for digital stethoscopes, power monitors and home health environmental monitors, such as cuff-less blood pressure monitors, pregnancy monitoring and remote electroencephalogram (EEG) monitoring.

The group is also working with FDA, along with other standards organizations, on the agency's nascent Precertification (Pre-Cert) Program to help figure out what certified standards used by companies in the program could ensure trust in their software design processes. *(Also see "'Excellence' In Health-Software Design: US FDA Taps Nine Firms To Figure Out What That Means" - Medtech Insight, 26 Sep, 2017.)*

"We feel this is really important because many other countries follow FDA," said Kirwan. "If FDA does approve this Pre-Cert program, I can imagine other countries doing the same. Why? It's the same people who want to go through regulatory clearance who want to do it in multiple countries that are asking for similar precedence and they'll have it with the FDA."

Kirwan said the standards groups have also asked FDA to create a blog for the Pre-Cert Program that would allow their members to provide direct feedback to the agency.

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Will AAA's Nuclear Med Offerings Turn M&A Buzz Into A Deal?

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With the recent European approval of *Lutathera*, the first theragnostic radiopharmaceutical of its kind to achieve this milestone, it is no surprise that **Advanced Accelerator Applications SA** (AAA) is looking more alluring than ever as an acquisition target for a pharma player.

Indeed, prior to the Oct. 2 approval announcement, AAA's name was already churning around the M&A rumor mill when media reports suggested that Swiss pharma giant **Novartis AG** was in talks with the French company over a potential acquisition. *(Also see "Will Radiopharmaceutical Company AAA Be M&A Fodder For Novartis?" - Medtech Insight, 28 Sep, 2017.)*.

When asked by *Medtech Insight* if there was any basis to these reports, AAA CEO Stefano Buono, commented that "in general," there has been interest from pharma. However, he added that there is also an expectation from drug companies to see if a radioactive drug, like Lutathera, would really take off in the market and become as successful as a conventional cancer therapeutic.

Radiopharmaceuticals has not had huge commercial success so far, according to Buono. The first radioactive drug by Baxter, *Zevalin* (ibritumomab tiuxetan), was approved by the US FDA in 2002 and even though it had demonstrated much better results than its comparator in clinical trials, it didn't have any commercial success, said the AAA CEO. "This scared the clinical community away from this idea of using a radioactive drug to treat a patient," he said. Then in 2013, a Norwegian company called Algeta with a prostate cancer drug Xofigo (radium-223 dichloride) was acquired by Bayer for $2.9bn, just as sales of Xofigo were getting started in the US and Europe. *(Also see "Algeta and Bayer agree $2.9bn sweetened takeover " - Medtech Insight, 19 Dec, 2013.)* However, for all the high expectations pinned on this drug's market success, as reflected by the hefty merger consideration, it also did not take off as well as expected and UK's NICE rejected Xofigo because there was not sufficient evidence of its cost-effectiveness for use in the NHS. *(Also see "NICE turns down Bayer's Xofigo" - Medtech Insight, 25 Mar, 2014.)*.

For a potential pharma buyer to make any advances beyond the discussion phase, Buono said AAA will need to prove that its radioactive drugs "will be a huge commercial success," which he strongly believes the company will do.

Buono's confidence in Lutathera succeeding whilst other similar drugs haven't lies partly in the simplicity of the platform on which the therapy is based. "We've made the platform very simple so that it is easy for the user."

Lutathera (lutetium (^{177}Lu) oxodotreotide) is approved for treating "unresectable or metastatic, progressive, well differ-

AAA On The Rise

It is not just AAA's portfolio that would appeal to potential buyers. The company's statement income appears to back the commercial validity of the products it is selling. Its top-line has grown steadily year over year; from €69.9m in 2014 to €88.6m in 2015, and then to €109.3m in 2016. The upward trajectory has continued this year, with the French firm posting total revenues of €36.5m, above analysts' expectations of around €33.3m for the quarter. This represented a 32% sales increase in 2Q17 versus the same period a year earlier.

European commercialization of Lutathera, together with the expected US FDA approval in early 2018, should bring short- to mid-term gains and bolster revenue even more.

Likewise, since it listed on the Nasdaq in November 2015, AAA's stock price has been on the up; it started trading at $18.50 on Nov. 9, 2015 and reached $58.30 on Sept. 26 this year, the day before the media report of the Novartis talks was released. This M&A speculation gave a further boost to AAA's stock value, and buoyed by the Lutathera approval, the company's shares now trade at the mid-$60 level.

The mid-sized pharma, founded in 2002 by Italian academics as a spin-off from the European Organization for Nuclear Research, has 21 production and R&D facilities that manufacture both diagnostic and therapeutic molecular nuclear medicine products, and over 530 employees in 13 countries (Belgium, Canada, France, Germany, Israel, Italy, the Netherlands, Poland, Portugal, Spain, Switzerland, UK and US).

entiated, somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults." It belongs to a class of drugs called peptide receptor radionuclide therapy (PRRT) in which octreotide – a peptide with a very high affinity with somatostatin receptors – is paired with a radioactive material, which, in the case of Lutathera, is lutetium (^{177}Lu). Lutathera is administered like conventional chemotherapy through an infusion drop into the bloodstream. Once in the blood stream, the molecule binds to the somatostatin receptor expressed on the surface of NET cells. The receptor brings the Lutathera molecule inside the tumor, where the radioactivity emitted by the drug kills the rumor cell from within, whilst having little effect on neighboring cells.

The European approval of Lutathera was based on results of a Phase 3 study, NETTER-1, involving patients with advanced midgut NETs. These patients were randomized to receive treatment either with Lutathera plus 30mg of octreotide LAR (long-acting repeatable) therapy or with a 60mg dose of octreotide LAR alone. The study met its primary end-point, showing that treatment with Lutathera resulted in a risk of progression or death that was 79% lower than the risk associated with high-dose octreotide LAR.

"We are using radiation that is well-known in radiotherapy of tumors, but so far used mainly for treating local tumors, not metastatic tumors," said Buono. Lutathera enables this radiation to be delivered internally and in a targeted way so that it reaches metastasized cancer cells.

The approval of Lutathera means AAA can now offer a full theragnostic solution for NET patients; the company is already commercializing gallium-labelled somatostatin analogues for diagnostic PET imaging of NETs. NETSPOT (gallium ^{68}Ga dotatate) was approved by the US FDA in June 2016 and its European equivalent, SomaKit TOC, was approved by the European Commission in December 2016.

"This is characteristic of nuclear medicine to get two drugs from the same targeting molecule [for two applications]: one for diagnostics and the other for therapy. So we can couple the same targeting molecule with gallium or lutetium; we use NETSPOT/SomaKit TOC to first diagnose the tumor, then Lutathera if it is determined that the patient needs therapy," said Buono. The diagnostic can also be used later for monitoring the patient to see if there is a recurrence of cancer.

AAA is planning to use this "simple but effective" technique of combining a single targeting molecule with radiation for diagnosing and treating other cancers. This includes prostate cancer, where AAA is currently investigating two candidates - 177Lu-PSMA-R2 and 68GA-PSMA-R2 – for treating, imaging and monitoring the disease. Again, lutetium is the radioactive isotope of choice for treatment and gallium for diagnostics; however, the targeting peptides will have a high-binding affinity for prostate-specific membrane antigen, a receptor on the surface of prostate cancer cells.

The firm's pipeline also includes using antagonist bombesin analogues, targeting gastrin-releasing peptide receptors, for diagnosing and treating gastrointestinal stromal tumors.

While the concept might seem simple enough, nuclear medicine is a far more complex business than conventional pharma companies would expect, warned Buono. " The logistics for the manufacture and supply of radiopharmaceuticals is very complicated and this is something that pharma companies, without experience of these products, cannot digest," he told *Medtech Insight*.

On the other hand, AAA already has over 15 years' experience of manufacturing and handling these types of drugs that have very particular properties, such as having only 10 hours of shelf life. "We deliver every day more than 1,000 doses to patients to over 200 patients, and that's the daily standard. We have this incredible know-how in daily manufacturing and delivery of the dose," he said. This expertise, Buono believes, will work to AAA's advantage of making Lutathera a commercial success – and potentially make the company even more attractive to industry suitors.

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MDxHealth Gears Up For Major EU Growth

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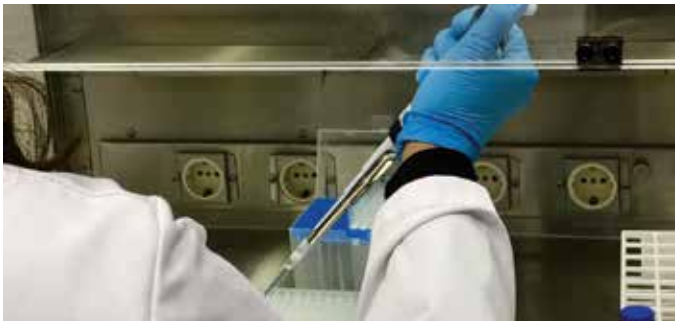

Cancer diagnostics firm **MDxHealth** has expanded its European lab testing capabilities with the acquisition of a larger facility in Nijmegen, Netherlands. The new center at the health-tech corporate park, Novio Tech Campus, broadens the company's service testing for *SelectMDx*, an mRNA, urine-based test to assess a patient's risk of prostate cancer and thus help determine whether he would benefit from a biopsy. The test can also be used to assess the probability for high-grade versus low-grade disease.

MDxHealth, a EuroNext-listed company, launched SelectMDx globally in April 2016 *(Also see "MDxHealth expects to be key Dutch provider of urine-based prostate cancer testing" - Medtech Insight, 13 Oct, 2015.)* and tested close to 1,200 patients in the first half of 2017, an increase of 319% year-on-year. The test is one of two products currently offered by MDxHealth for prostate cancer testing. The company's flagship product ConfirmMDx, uses MDxHealth's proprietary technology platform Methylation-Specific-PCR (MSP) to assess methylation markers for prostate cancer with tissue biopsies. *(Also see "MDxHealth Prostate Cancer Test Identifies Increased Risk of Cancer Recurrence" - Medtech Insight, 28 Mar, 2017.)*

In the company's 2017 half year results, MDxHealth reported total revenue of $24.3m, up 87% from last year, largely driven by $12.1m net revenue from a one-time buy out of the company's patents for colorectal cancer by Exact Sciences. ConfirmMDx accounted for 93% of product revenues compared to 98% last year, and SelectMDx contributed for approximately 35% of the total worldwide tests done across all products.

Speaking at the company's new research lab, Jan Groen, MDxHealth CEO told *Medtech Insight* test volumes had grown 44% in the first half of 2017, using the same number of sales reps on the field as last year. "In 2018 we plan to grow the Select product in the European market and focus on reimbursement and getting the test in the respective clinical guidelines. That can only be done by the support of enough scientific data and we're currently running studies in Spain, France, Germany and additional ones in the Netherlands to support this inclusion," he said.

The location of the new European HQ will support opportunities for MDxHealth to further collaborate with the Radboud University Medical Center in Nijmegen, home of spinoff molecular diagnostics company **NovioGendix** which was acquired by MDxHealth in 2015. *(Also see "MDxHealth Eyes 2016 Liquid Biopsy Prostate Cancer Test Launch With NovioGendix Buy" - Medtech Insight, 16 Sep, 2015.)* "For us to have MDx on the campus is a great partner for us to do all kinds of other projects," Jack Schalken, professor of experimental urology at Radboud University Nijmegen Medical Center and co-founder of NovioGendix said. "We focused initially on prostate, bladder and kidney cancer but the strength of the hospital is of course that we have patients and we have biorepositories for all types of research. MDxHealth as a company can then standardize technology which is the one thing that most of us researchers don't like but the prime motto of my academic hospital is to make a significant impact on healthcare."

"When we acquired NovioGendix we were only five people and today we are twenty-five," said Groen. "There was no opportunity for growth at our location in Belgium and we needed a space to really grow the company. I was a little hesitant to begin with but at the end of last year we saw a lot of interest in the Select products and we wanted to prepare for the development of new products for other indications that we want to launch in the European market and to do that we needed a bigger space."

Groen said a lot of education and effort was involved to "hammer home" the benefit of the prostate cancer tests to urologists. "They are constantly being inundated with new, innovative diagnostic products, not just by us but by many other companies," he said. "But if you look at overall units that we are selling, we're the market leader compared to other players in the space. This is also driven by the fact we offer a broader portfolio so we can serve the urologists pre-biopsy and once they've done a biopsy procedure so they know what to do next."

MDxHealth has also rolled out a third commercial diagnostic test, *AssureMDx* liquid biopsy urine test for bladder cancer, that is currently only available on the US market which is believed to be worth around $500m. Similar to SelectMDx and ConfirmMDx, the product is a combination of methylation and mutation testing and a PCR-based assay. The test aims to fill a gap in the clinical world for a non-invasive diagnostic bladder cancer test.

In the future, Schalken said MDxHealth's cancer products would have technology for increased specificity and sensitivity. "We need to focus on the product because right now with our prostate cancer tests for example they are being used for men with a 'grey zone PSA' - so that's a serum PSA between 2.5 and 10," he explained. "The next step for the company is to develop a tool for the general practitioner who can then identify more aggressive cancers just lying in the low ranges. The reason we currently can't do population based screening for prostate cancer is because of the danger of over diagnosis. If we can really find aggressive cancers early, then that's when we can really make a difference in prostate cancer mortality."

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US APPROVALS ANALYSIS: Cook Churns Out 510(k)s In Q3

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Cook Group Inc. averaged more than one 510(k) clearance per week last quarter, leading all firms in Q3 and pulling closer to perennial leader Medtronic for the full 2017.

The company, including all subsidiaries, has logged 45 substantial-equivalence decisions this year through September. That puts the privately held firm just shy of the total achieved so far by Medtronic's full operations for the year so far (49 clearances) and ahead of Siemens, with 39 clearances.

The performance represents a significant acceleration in Cook's regulatory productivity – triple the number achieved by the firm through the first nine months of 2015, and up from 27 through September 2016, according to *Medtech Insight*'s Approvals Tracker.

Cook Group has a diversified device business with products ranging from endovascular and peripheral implants to endoscopy and surgical equipment, to specialized tools for otolaryngology and urology, as well as biologic tissue grafts. The firm gained 19 clearances in the third quarter ending Sept. 30, including for a "peal-away" introducer set for percutaneous entry of balloons and catheters; a nasal pancreatic drainage set that applies an indwelling catheter for temporary endoscopic drainage of the pancreatic duct through the nasal passage; and the Biodesign Parastomal Hernia Repair Graft for patching weak areas in soft tissue – in particular, to repair parastomal hernias.

510(k) clearances are the basis for the medtech sector's iterative development cycle. Although what goes into a 510(k) submission can vary significantly by product, the number of 510(k) clearances a firm gets through FDA is one measure of its regulatory and R&D productivity, as well as the overall breadth and heft of its offerings.

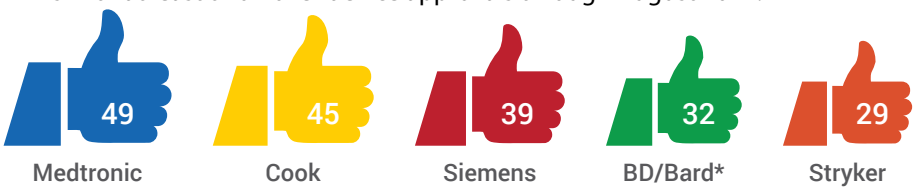
Cook tied with GE Healthcare with the third-most clearances last year, and the firm did not make the top 5 in 2015.

FDA cleared a total of 241 510(k)s in September and 781 in Q3, down from 839 in Q2. So far, the agency is just ahead of its 2016 510(k) volume, with 2,361 submissions cleared in the first nine months of this year compared to 2,209 in the same period last year.

FIGURE 1

510(k) Clearance Leaders, January-September 2017

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

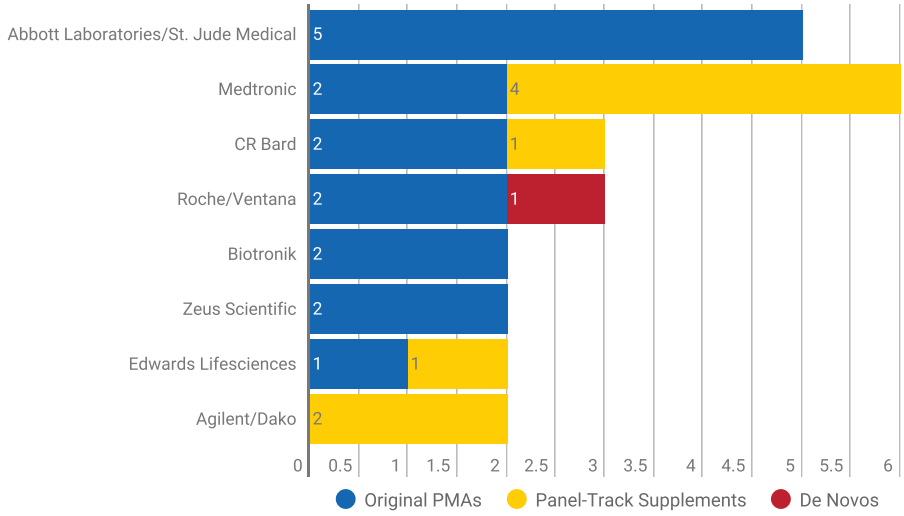


**BD/Bard count includes clearances from Becton Dickinson and current subsidiaries, plus CR Bard - the firm BD is currently in the process of acquiring.*

Source: Medtech Insight's Approvals Tracker

FIGURE 2

Novel-Device Approval Leaders, January-September 2017

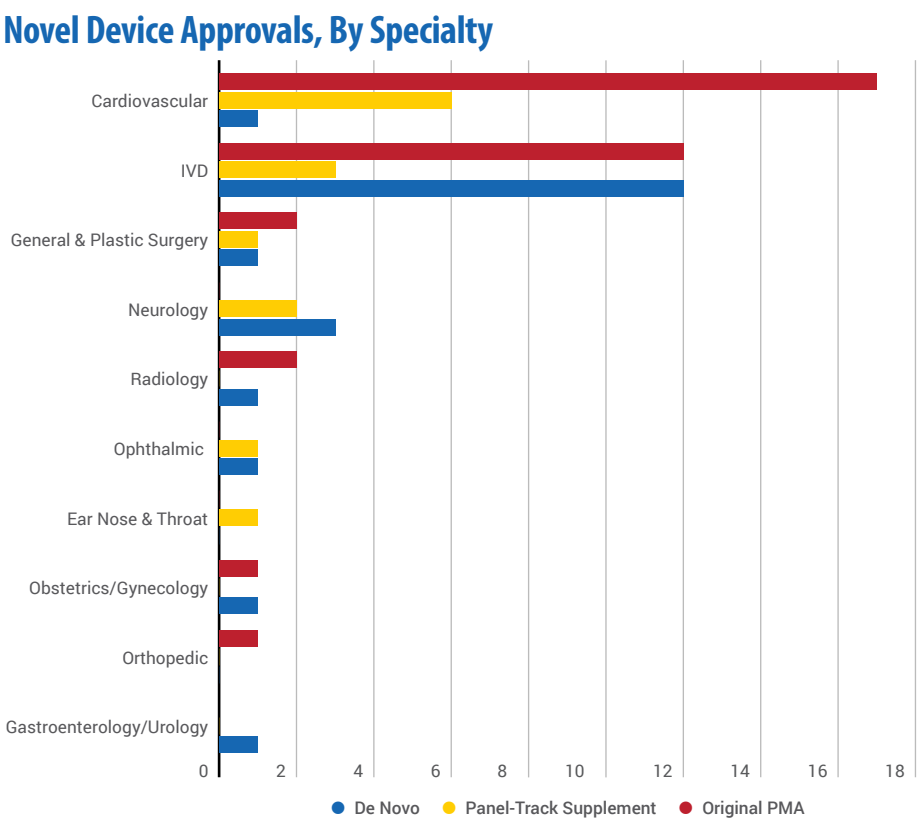


Medtech Insight's Approvals Tracker

Notable devices cleared in the past month include:

- **Abbott Laboratories Inc.**'s *Confirm Rx* insertable cardiac monitor, cleared Sept. 29 to assess patients potentially experiencing arrhythmias. It's intended to compete with Medtronic's successful *Linq* monitor, but the programmer intended to be used with the monitor must gain a PMA approval before US launch.
- Cefaly Technology's *Cefaly Acute* external trigeminal nerve stimulation (e-TNS) device, cleared Sept. 15 for treating patients experiencing a migraine. A version of the device was cleared in 2016 to help prevent migraines in certain chronic sufferers, but the acute-phase treatment labelling represents a tenfold larger market, the Belgium-based company says.
- Carrot Sense Inc.'s *Carbon Monoxide Breath Sensor System*, cleared Sept. 29 as an over-the-counter, *Bluetooth*-enabled device intended for use with a smartphone app as part of smoking cessation programs.

FIGURE 3



Medtech Insight's Approvals Tracker

- ClaroNav Inc.'s *NaviENT* computer-assisted 3-D navigation system for surgery to treat sinusitis, cleared Sept. 1.

ABBOTT NABS ANOTHER PMA

In addition to recording a notable 510(k) clearance last month, Abbott also continued its spate of high-risk device approvals via original PMAs with the Sept. 27 approval of the *Freestyle Libre Flash* as the first continuous glucose monitoring system labeled for use without any need for fingerstick calibration. *(Also see "First Anti-Addiction App Approved In The US" - Medtech Insight, 14 Sep, 2017.)* The device adds a new competitive dynamic to the CGM market that has principally been a battle between Medtronic and Dexcom.

The Libre Flash follows two original PMA approvals for Abbott-owned brands in August – for the *HeartMate 3* left-ventricular assist system and for the *RealTime IDH2* companion diagnostic to inform treatment with a drug that targets relapsed or refractory acute myeloid leukemia. *(Also see "US Approvals Analysis: Abbott Leads Another Strong Month For Novel Approvals" - Medtech Insight, 13 Sep, 2017.)* That makes for five such approvals this year, the most of any company.

But Medtronic has inched ahead in the count of novel-device and indication approvals (original PMAs, panel-track supplements and *de novos*) with six such approvals this year, including two panel-track supplements achieved in September. In particular, the device giant touted a Sept. 27 approval for adding a destination-therapy indication to its *HeartWare HVAD* left-ventricular assist system, and a Sept. 29 expanded indication for its *Endurant II* stent-graft system.

Two other firms also gained multiple novel-device approvals last month. On Sept. 19, **Zeus Scientific Inc.** recorded parallel original PMA approvals for its *Zeus Elisa Parvovirus B19*IgG and IgM test systems to streamline lab testing for parvovirus B19, which causes "fifth disease."

In addition, **Agilent Technologies Inc./ Dako AS** gained two companion diagnostic panel-track supplement approvals in September – a Sept. 15 go-ahead for its *PD-L1 IHC 28-8 PharmDx* assay to support use of the drug *Opdivo* (nivolumab) for urothelial carcinoma and squamous cell carcinoma of the head and neck, and a Sept. 27 approval for *PD-L1 IHC 22C3 pharmDx*, expanding its labeling into gastric cancer treatment with *Keytruda* (pembrolizumab).

Overall, FDA's four original PMA approvals in September bring the total after three quarters to 35, ahead of pace compared to the user-fee-era record year 2015. *(Also see "FDA Hits User-Fee-Era Record For 'Novel' Devices: A New Normal?" - Medtech Insight, 14 Jan, 2016.)* The four panel-track supplement approvals bring the total for that category to 14, a little behind last year's record pace. *(Also see "US Approvals Analysis: 2016 Another Record Year For FDA Novel Device Approvals" - Medtech Insight, 13 Jan, 2017.)* The one *de novo* classification last month brings that January-September total to 21, also a record pace.

CLINICAL SPECIALTIES: NEUROLOGY MAKES A DENT

Broken down by clinical specialty, cardiovascular devices – as usual – far outpaces approval volumes for other specialties. Only *in vitro* diagnostics, when viewed as a crosscutting category, surpasses it.

Among other specialty areas, novel neurology devices have attracted the highest number of approvals this year so far with five. Most recently, Pear Therapeutics gained a *de novo go-ahead Sept. 14* for its *reSet* mobile app to treat substance abuse. *(Also see "First Anti-Addiction App Approved In The US" - Medtech Insight, 14 Sep, 2017.)* Approved based on a randomized study, Pear says it is the first piece of standalone software that "has ever been cleared by the agency to treat any disease." *(Also see "'Excellence' In Health-Software Design: US FDA Taps Nine Firms To Figure Out What That Means" - Medtech Insight, 26 Sep, 2017.)*

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OUS APPROVALS ANALYSIS: Abbott Announces Three Glucose Control CE Marks; iVascular Earns Five Approvals In India

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Abbott Laboratories Inc. leads September's list of approvals from outside the US, according to *Medtech Insight's* Approvals Tracker, with six approvals – all CE Marks for glucose control products.

According to Abbott's website, the *LibreView* data management system now has a CE mark for both type 1 and type 2 diabetes. The web-based data management platform is compatible with the *FreeStyle Libre Pro* blood glucose monitor as well as most major blood glucose meters, according to the company. The firm also reported that the *FreeStyle Auto-Assist* software has a CE mark for both type 1 and type 2 diabetes. FreeStyle Auto-Assist includes variety of data tools to evaluate data from glucose meters including Abbott's *FreeStyle Lite*, *FreeStyle Freedom Lite*, *FreeStyle InsuLinx*, *FreeStyle Freedom*, and *Precision Xtra* systems.

Also, the *FreeStyle Precision Pro* blood glucose and beta-ketone monitoring system for health professionals now has a CE mark, according to operators manual available from the UK's National Health Service. The FreeStyle Precision Pro is intended for in vitro diagnostic use for the quantitative measurement of glucose in fresh capillary whole blood and of ketone (betahydroxybutyrate) in fresh capillary whole blood samples. It is not indicated for diagnosing diabetes, but for health professionals to monitor their patients' progress in managing diabetes.

September was a big month for Abbott's diabetes business. On Sept. 27, the US FDA approved the mobile *FreeStyle Libre Flash* continuous glucose monitoring system, the first CGM approved to help adult diabetes patients to directly make treatment decisions without calibration from a blood sample. The FreeStyle Libre Flash earned a CE mark in 2014. It eliminates the need for users to regularly draw blood from their finger by reading glucose levels through a sensor that can be worn on the back of the upper arm for up to two weeks.

IVASCULAR MAKES BIG MOVE INTO INDIA

Barcelona-based **iVascular SLU** leads September's list of device approvals outside the US and Europe with a series of approvals for its coronary and peripheral products in India, announced September 20.

The regulatory approvals in India, which represent the company's first move into Asia, include the *Angiolite* coronary sirolimus-eluting cobalt chromium stent featuring a proprietary nanotechnology biocompatible coating called *TransferWise*. Results of the 103-patient ANCHOR trial, published by *Catheterization & Cardiovascular Interventions* in July, show Angiolite is safe and yields high rates of strut coverage, modest degrees of neointimal hyperplasia, very low rates of strut malapposition with no in-stent binary restenosis and almost no in-stent late-lesion loss.

iVascular sees an opportunity in the Indian stent even though Indian's National Pharmaceutical Pricing Authority recently announced caps on the prices manufacturers can charge for coronary stents that will cut the price stents by over 75%. *(Also see "India's Stent Price Slash Creating Climate Of Fear, Foreign Device-Makers Say" - Medtech Insight, 15 Mar, 2017.)* Currently, The Indian coronary stents market is dominated by Abbott Laboratories Inc. and Medtronic PLC.

India's government has also approved iVascular's *Essential* coronary paclitaxel-coated balloon catheter and *Luminor* a similar balloon-catheter designed for treating peripheral disease. Both feature TransferTech to guarantee the drug's stability and prevent drug-particle loss during navigation. Luminor is supported by results of the 172-patient EFFPAC randomized trial, which showed Luminor produces superior patency, late-lumen loss, and target lesion revascularization rates compared to non-drug-coated balloon catheters, according to the company.

The company is also set to launch the *iVolution* an open-cell, self-expanding nitinol peripheral stent and the *Restorer* cobalt-chromium peripheral stent systems into the Indian market following regulatory approval there, the world's fourth largest med-tech market.

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OUS Approvals

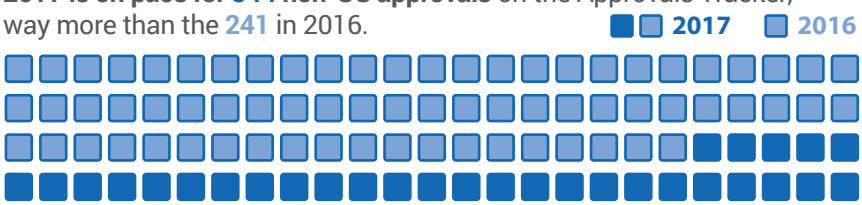
SEPTEMBER 2017

Cardiovascular devices and devices to treat diabetes dominated this month's list of OUS approvals.

24 TOTAL APPROVALS
including
16 CE Marks

The 24 approvals in September were **below average** for 2017, but one more than the 23 OUS approvals in September 2016.

2017 is on pace for 344 non-US approvals on the Approvals Tracker, way more than the 241 in 2016.



Product Categories
24 TOTAL

11 Cardiology

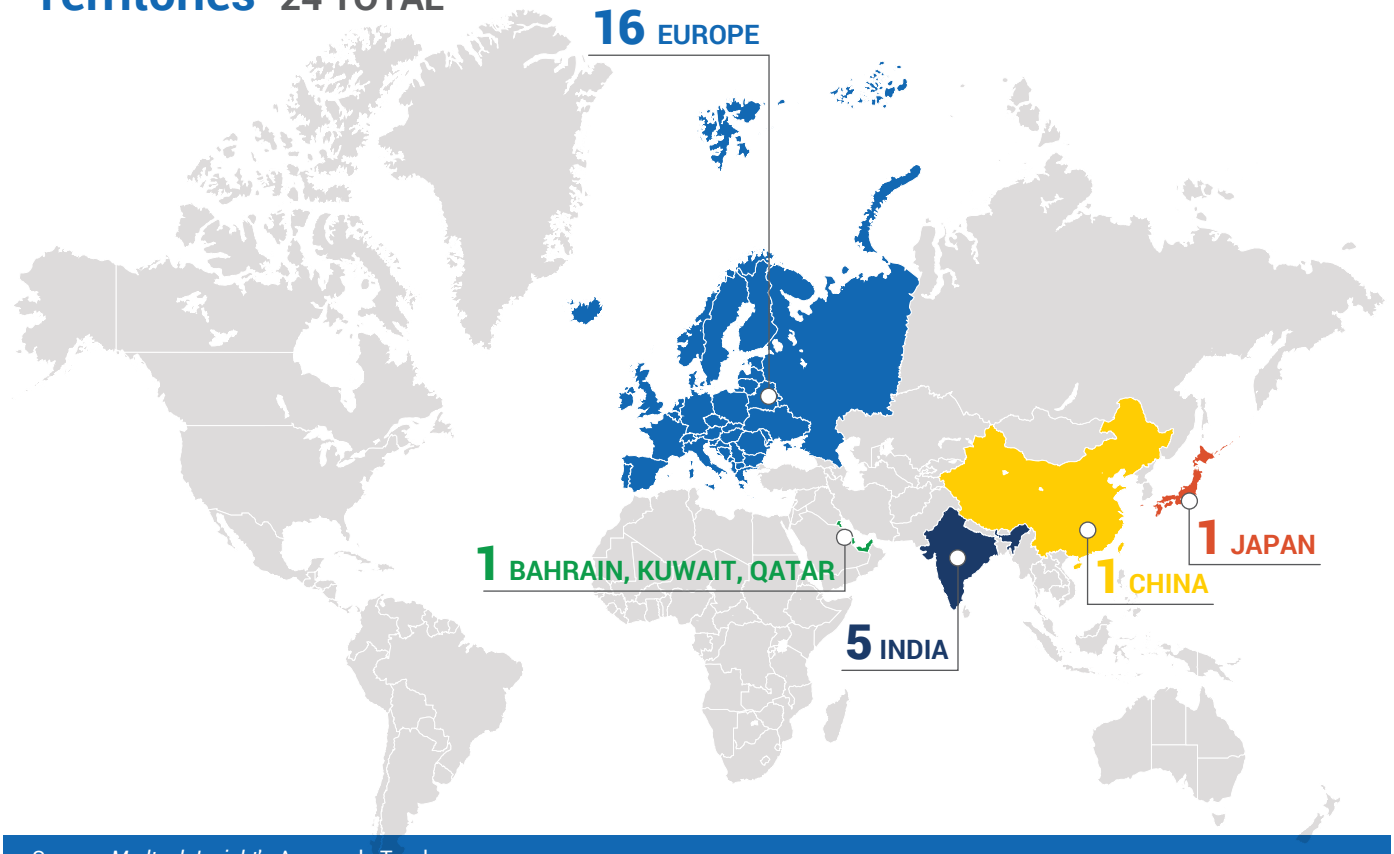
8 Diabetes

2 In Vitro Diagnostics

2 Surgery

1 OB/GYN

Territories 24 TOTAL



Source: *Medtech Insight*'s Approvals Tracker

START-UP SPOTLIGHT: Arkis BioSciences, Endexo-Boosted Ventricular Drainage Catheter Reduces Obstructions

BOB KRONEMYER bkronemyer@frontier.com

Unlike traditional catheters that drain cerebrospinal fluid from the brain to relieve pressure when treating intracranial hypertension in an intensive care unit (ICU) setting, the *CerebroFlo* external ventricular drainage (EVD) catheter from **Arkis BioSciences Inc.** has the added benefit of being impregnated with *Endexo* (developed by Canadian-based **Interface Biologics Inc.**), an antiocculsive agent previously commercialized for vascular access catheters.

"Endexo is not a drug-eluting catheter, which is an advantage," Arkis CEO Chad Seaver told *Medtech Insight*. "Endexo is a polymer additive. It is not a coating that depletes over time. It also does not gradually elute. Hence, concerns about materials or drugs dissolving in the brain are alleviated."

In laboratory studies, Endexo has shown to dramatically reduce the incidence of thrombus formation, which can potentially reduce catheter obstructions, Seaver said. In addition, hospitals have reported that Endexo-containing peripherally inserted central catheters (PICCs or PIC lines) achieve more than a 70% reduction in catheter obstructions as well as about an 86% reduction in associated infections.

Arkis has exclusively licensed Endexo from Toronto-based Interface Biologics for central nervous system applications. The external CerebroFlo catheter is a brain catheter used in cranial neurosurgery to drain cerebrospinal fluid from a ventricle of the brain to reduce intracranial hypertension.

"High brain pressure can occur for a number of reasons, ranging from head injury to hemorrhagic stroke to hydrocephalus (excessive brain fluid that results in elevated intracranial pressure)," Seaver explained.

Nearly 200,000 external ventricular drain (EVD neurosurgeries are performed yearly in the US, all of which are candidates for the CerebroFlo system, which received 510(k) clearance in August with CE-mark projected for 2018. This represents an annual market opportunity of more than $100m, according to the company.

ARKIS BIOSCIENCES INC.
1 Momentum Way
Knoxville, TN 37920

Phone: (844) 247-5383

Web Site: www.arkisbiosciences.com

Contact: Chad Seaver, CEO

Industry Segment: Neurosurgical

Business: Minimally invasive surgical instrumentation and next-generation implantables for advancing neurosurgery

Founded: June 2013

Founders: Chad Seaver; James Killeffer; Chris Arnott

Employees: 10

Financing to Date: $6m

Investors: Innova Memphis; Angel Capital Group; Lighthouse Fund; Individual Angel Investors

Board of Directors: Ken Woody (Innova Memphis); Clif Moyers (RbM Services LLC); Chad Seaver; James Killeffer

Scientific Advisory Board: James Killeffer, (University of Tennessee, Knoxville); Michael DiLuna, (Yale School of Medicine); Richard Penn, (formerly of Rush Medical College, Chicago); Gentry Savage, (East Tennessee Children's Hospital, Knoxville); Kevin Sheth, (Yale School of Medicine); Lawrence Shuer, (Stanford University School of Medicine); Karl Sillay, (Nashville Neurosurgery Associates, Nashville); Marvin Sussman, (formerly of Cordis Corp.)

BACKGROUND

Arkis was formed in 2013 to tackle existing challenges in treating hydrocephalus, said co-founder James Killeffer, a neurosurgeon in private practice in Knoxville, Tennessee. The third co-founder, Chris Arnott, an engineer and former patent examiner, was instrumental in developing the company's intellectual property portfolio. Seaver, an engineer by training, explained some of the technological challenges Arkis faced in developing the device.

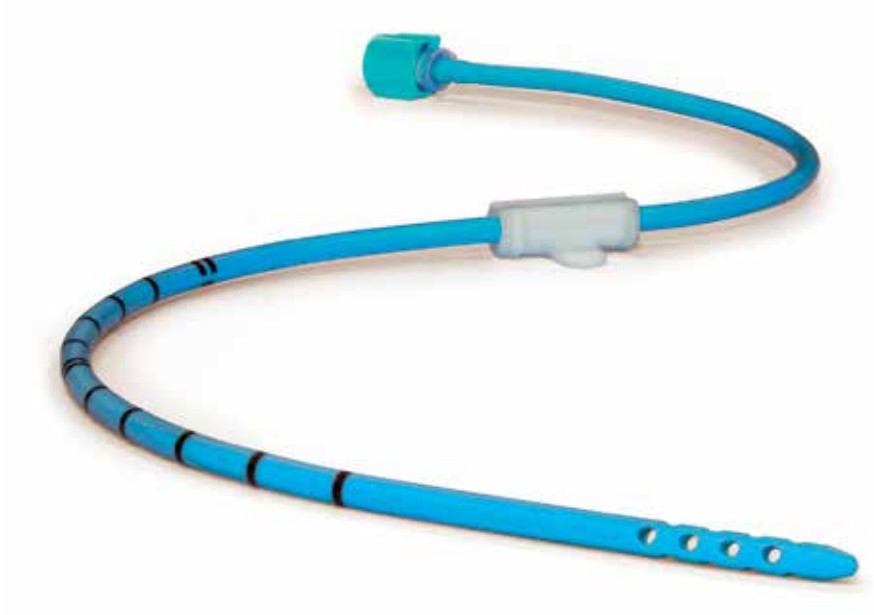
"We created minimally invasive surgical instrumentation to help make hydrocephalus shunt procedures one third less invasive, along with new catheter technology to incorporate Endexo into a brain catheter," Seaver said. "The safety and efficacy testing necessary for the catheter was quite an ordeal, including X-ray photoelectron spectroscopy for the analysis and development of adding Endexo, which may reduce catheter obstructions by inhibiting protein adhesion and activation."

Seaver began working at **CTI Molecular Imaging Inc**. in 2000 as an engineer and eventually became a business manager. When the company was acquired by **Siemens AG** in 2005, Seaver stayed on as a senior manager for business development until the founding of Arkis in 2013.

Currently, Arkis has six patents issued and over 20 patents pending. Other than its licensing agreement with Interface Biologics, Arkis will not be sharing royalties and/or revenues with any another entity.

FIG. 1

Arkis Biosciences' CerebroFlo EVD Catheter



Arkis Biosciences

"We created minimally invasive surgical instrumentation to help make hydrocephalus shunt procedures one third less invasive, along with new catheter technology to incorporate Endexo into a brain catheter," Seaver says.

The single-use, disposable CerebroFlo system consists of a 10 French polyurethane catheter that is 35 cm long, along with common accessories to support a ventriculostomy. A neurosurgeon, who performs a ventriculostomy, first makes a burr hole in the skull, then implants the catheter into a ventricle of the brain. The catheter is then connected to an external fluid collection system.

The entire procedure typically takes less than one hour.

"There is no learning curve, because all neurosurgeons know how to insert an EVD catheter," Seaver said.

Following the procedure, the patient rests in an ICU with the catheter typically remaining in the brain for seven days and with a daily draining of cerebral fluid in the 0.25-liter range.

"For several reasons, the brain can accumulate excess fluid, and in some cases the fluid is artificially reduced to compensate for brain swelling," Seaver said.

The company's three major competitors make conventional external EVD catheters without Endexo to treat intracranial hypertension: **Medtronic USA Inc.** (*VentriClear*), **Integra LifeSciences Holdings Corp.** (*Bactiseal*) and **Natus Medical Inc.** (*TraumaCath*).

"We have shown a 99% reduction in thrombus formation in-vitro compared to a representative traditional catheter," Seaver said.

Furthermore, although the catheters from both Medtronic and Integra have antibiotics impregnated within, Arkis' catheter does not elute drugs, thereby avoiding antibiotic resistance. However, a large hospital study from Ottawa, Canada, reported an 86% reduction in infection rates using Endexo vascular catheters versus historical catheters without Endexo, Arkis said.

The CerebroFlo catheter, which is priced competitively to current catheters and is covered under prevailing cranial procedures, began selling nationwide this month at the annual Congress of Neurological Surgeons in Boston. The company will be using a combination of a direct sales force and distributors. European sales are expected to start by the end of 2018 through distributors, and are also already reimbursable.

The $6m raised to date by Arkis constitutes three completed rounds of financing and one partial round: an initial seed round of $600,000, funded by angel investors, closed in April 2013; a second seed round of $400,000, also capitalized by angel investors, concluded in June 2014; a Series A of $3.4m, led by Innova Memphis, closed last June; and $1.6m toward a Series B of up to $8m via undisclosed financing is scheduled to conclude in Q1 2018.

Other than its Endexo licensing agreement, Arkis has no partnerships. However, the company is currently exploring strategic alliances for sales and marketing. The most likely exit strategy is acquisition by one of the leading catheter players, as soon as in two years.

"We will also continue to proliferate Endexo into other CNS catheters, foremost shunt catheters and subdural drains," Seaver said.

Meanwhile, Arkis will continue marketing its *Single Pass* Tunneling Guidewire, which was FDA listed in November 2016. The minimally invasive tunneling instrument for routing ventriculoperitoneal (VP) shunt catheters from the brain to the abdomen in a single pass largely eliminates the need for a third surgical incision site for permanent drainage from an implanted shunt.

"The Single Pass makes the procedure potentially one-third less invasive," Seaver explained.

Arkis also provides surgical tools for general and plastic surgeries, including minimally invasive tunneling instrumentation.

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