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Roche Exits Insulin Pumps Segment In India

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Roche Diagnostics, the market leader in India's IVD industry, has confirmed it has moved out of the insulin pumps segment in the country. According to the company, the insulin pump is not extensively used in India as a solution for people with insulin-dependency.

The Swiss multinational said it would like to "focus" on providing people with diabetes self-monitoring solutions that will help them have a "good quality of life".

"We firmly believe that with regular self-monitoring, the vast population of people with diabetes in India can keep their blood glucose levels in check and lead normal lives, without becoming insulin-dependent. Our exiting the insulin pumps segment in India is to fully concentrate on the SMBG (self-monitoring of blood glucose) segment," Sidhartha Roy, business unit head (diabetes care), Roche Diagnostics India, told *Medtech Insight*.

Roche's Accu-Chek Spirit Insulin Pump has not been available in India since 2011, but the company has been servicing insulin-dependent diabetics in India with the Accu-Chek Combo system right up "until a few months ago".

Roche confirmed that the Accu-Chek Combo system will not be available in India hereon. The Accu-Chek Combo system combines a blood glucose meter with an insulin pump that can exchange data in both directions via Bluetooth wireless technology; it supports a more targeted therapy management and also permits discrete insulin administration without the need to touch the pump, a 2012 Roche statement notes.

The company's latest generation insulin pump, Accu-Chek Insight, has not been launched in India, it said.

Asked whether Roche would continue to assist/ service patients who have been using its insulin pumps in India or whether they had been transitioned to other products, Roy said: "Simultaneous to the decision of exiting the insulin pumps business in India, we initiated the process of transitioning our pump users to another similar product available in the country. The transition process has been completed with utmost care".

COST, SERVICE SUPPORT

Some experts say that while insulin pumps offer significant convenience and can deliver more accurate amounts of insulin

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Adverse events: trends and tribulations
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US FDA is inundated with adverse events through its Medical Device Reporting system, yet several industry experts say the industry overall may be underreporting adverse events, while some firms are overreporting. Also, warning letter trends point to problems. Check out our feature, and our new FDA Warning Letters Data Tracker.

Medtechs organize in India
http://bit.ly/2dGGmaR

Leading medtech players have formed the Medical Technology Association of India, or MTaI, to step up penetration into the Indian market.

IPO on the up in Q3
http://bit.ly/2dtDISZ

Q3 saw a rise in the volume of initial public offerings, sparking hopes for a potential IPO rebound in 2016.

LDT promotion
http://bit.ly/2dJIlqp

Device-practice attorneys provide tips and precautions for laboratories advertising non-cleared or unapproved molecular-based diagnostics to avoid enforcement.

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Our weekly podcast, where *Medtech Insight* journalists discuss topics they are covering that impact the device and diagnostics sector.

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compared with the syringe, the cost factor has been a significant deterrent especially in emerging markets like India.

While the exact prices of insulin pumps in India could not immediately be ascertained, industry experts say they are in the region of INR200,000 ($2,999), excluding the associated recurring costs for insulin supplies and accessories. That is within the same price range as a Nano, the small car from the Tata group's stable in India.

Roche acknowledged that the factors attributing to the low use of pumps by insulin-dependent diabetics include the "relatively high cost" of an insulin pump and the "service support" required to maintain it.

"For India especially, service support has been a major factor, considering the vast geographical spread of the country," Roy said.

An expert with a frontline multinational devices firm told *Medtech Insight* that insulin pumps per se have not been a very viable business in India because of the "huge connect" required between patients and the company.

"The patient has to be 'owned' by the company; there is a huge service component and margins are not attractive," the expert said, adding that only few markets in the Asia Pacific are really feasible for such products in general.

Of the total population of people with diabetes in India, only 5% have type 1 diabetes and of this, less than 1% are reported to use insulin pumps; these pumps typically delivers insulin from a reservoir inside the pump to a patient's body using an infusion set and a tiny cannula.

BUILDING AWARENESS

While Roche's diabetes care business has seen lower worldwide sales in the first half of 2016, the Asia-Pacific and specific countries like Brazil, China and India have reported significant growth in the overall diagnostics business, an investor presentation in August indicated.

On whether the exit from insulin pumps in India is perhaps part of an effort to weed out the less sustainable businesses in the region, the company said that **Roche Diabetes Care** in India "strategically focuses" on offering self-monitoring solutions to people with diabetes, to enable them to lead normal lives.

"Our efforts are concentrated on building awareness amongst the young population of people with diabetes in India, so that their quality of life can be maintained with regular self-monitoring and specialist advice. This is the need of the hour for people in India, given the alarming levels of diabetes prevalence in the country," Roy added. Roche believes such awareness initiatives will also enable the healthy and young people of India to focus on healthy eating, fitness and regular checks of their blood glucose levels, to avoid diabetes due to lifestyle reasons.

There has been some past speculation that Roche may put its diabetes testing business on the block globally, though a news agency report in May this year quoted the top brass of **Roche Diagnostics Corp.** as underlining the group's commitment to the business and its growth potential.

Roche's awareness efforts in India are also in sync with the overall thrust of the Indian government in the area in view of the mounting burden of non-communicable diseases (NCD) in the country. India has initiated an integrated National Program for Prevention and Control of Cancers, Diabetes, Cardiovascular Diseases and Stroke focused on health promotion and prevention, strengthening of infrastructure including human resources, early diagnosis and management and integration with the primary health care system through NCD cells at different levels for optimal operational synergies. More recently, India's Ministry of Health and Family Welfare in collaboration with the WHO Country Office for India and other partners rolled out a mobile health initiative for the prevention and care of diabetes.

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FDA Tempers Accuracy Standards For Hospital Glucose Meters In Final Guidance

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FDA finalized two guidance documents to set out distinct pre-market expectations for blood glucose meters in two different settings: point-of-care hospital-based testing and over-the-counter patient self-testing.

The agency made a key change to the recommended standards for proving sufficient accuracy of a hospital-based glucose meter in the point-of-care (POC) guidance.

Draft versions of the two guidance documents, which are focused on conventional single-test systems rather than continuous glucose monitors, were issued in January 2014. The draft document that focused on POC hospital blood glucose systems, in particular, raised serious concerns from industry, laboratory directors and clinicians. In particular, they argued that FDA's proposed accuracy standard thresholds were so high that it could drive companies out of the market. Critics also convinced members of Congress to chime in against FDA's proposals.

FDA's goal with the two guidance documents is to end the long-term practice of glucose systems being approved based on pre-market assessments to support self-use by diabetics, rather than for specific populations in hospitals, where there are more factors interfering with accurate glucose testing and where patients may be more vulnerable to inaccurate results, according to the agency.

Laboratorians and manufacturers, among others, said they agreed with the need to

tighten standards for hospital systems, but many argued that the 2014 draft guidance went too far.

FDA appears to have responded to that criticism. The accuracy standards in the final POC system guidance have been adjusted closer to the levels recommended by stakeholders.

Specifically, the draft guidance said that meters should demonstrate that ***99%*** of all values are within plus-or-minus ***10%*** of the reference method at glucose concentrations of 70 mg/dL or more, and within plus or minus ***7 mg/dL*** for concentrations below 70 mg/dL. And, the draft said, ***all*** results should be within ***20%*** of the reference method for a concentration of 70 or more, and plus-or-minus 15 mg/dL below 70.

But, according to FDA's final version, only ***95%*** of values need to be within plus-or-minus ***12%*** or ***12 mg/dL***. And ***98%***, rather than all, results should be within ***15%*** or 15 mg/dL. These revised cutoffs are closer to, though not precisely the same, as standards established by the Clinical and Laboratory Standards Institute in 2013 that were highlighted as a more reasonable option by multiple stakeholders commenting on the draft guidance.

One group that was critical of the draft guidance was the American Association for Clinical Chemistry. The group says it is still assessing the final versions. "AACC is currently reviewing the final guidance and we look forward to working with the FDA to ensure that patients continue to have access to quality, timely patient testing," said Molly Polen, the association's director of communications.

The final POC guidance also includes more details on what a company can do to still gain clearance even if an assay does not meet these criteria.

"Though we expect that [blood glucose monitoring systems] will be able to meet this criteria, there may be instances where meters may be determined to be substantially equivalent when performance does not meet these criteria because, for example, other features of the meter or its setting-of-use provide benefits that compensate for different performance," the final guidance states. "In instances where your BGMS is unable to meet these criteria, you should provide a clinical justification for all test results, including those that exceed the above-mentioned criteria, and describe why the potential for that error would not affect patient safety when extrapolated to the intended-use setting."

In September 2014, **Nova Biomedical Corp.**'s *Nova StatStrip* became the first blood glucose monitoring system FDA-cleared and CLIA-waived specifically for professional, point-of-care use in all hospital patients, including intensive-care patients. But FDA did not employ the accuracy cutoffs that were proposed in the draft guidance to support that clearance decision.

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EU Regulation Implementation Deadlines And Other Pressing Issues

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What do I have to do and by when? That is one of the key questions manufacturers are asking themselves in the context of the forthcoming EU Medical Device and IVD Regulations, an industry insider said at a recent London conference.

Addressing the Annual Regulatory Conference of the Association of British Healthcare Industries, Thecla Sterk, manager of regulations and industrial policy at EU trade association Medtech Europe, highlighted several basic questions that medtech manufacturers have, including when the revamped medical device Eudamed database will be ready and when notified bodies will be ready to issue certificates against the requirements of the new regulations.

Sterk presented the following slide to the medtech sector to better understand at a glance the timelines ahead:

When it comes to what Medtech Europe is doing, priorities include a detailed analysis of the Medical Device and IVD Regulations, including understanding what will change from the current directives and understanding what needs to be done by when. Companies should develop an implementation toolkit for members and running workshops and webinars, for example, Sterk said.

Also high on the agenda for industry should be actively participating in European Commission working groups on the new Eudamed database. Companies will also need to analysis of what is needed in the context of future secondary legislation. This will include work focused on the future implementing and delegating acts, which will need to be drafted and adopted to support the regulations, as well as those issues that need to be addressed outside of secondary legislation.

John Brennan, director of regulations and industrial policy for Medtech Europe, highlighted at the meeting the initial areas that require the most immediate clarification in the forthcoming Medical Devices and IVD Regulations.

For the MDR, Brennan said, more information is most urgently needed for:

- Implementation timings;
- Clinical Evaluation; and
- Labeling.

For the IVDR, he said, the key near-term issues are:

- Classification;
- Clinical evidence; and
- Conformity assessment.

When it comes to the timing of implementation, Brennan says clarity is needed as soon as possible so industry can prepare to comply with the new rules as efficiently as possible.

Clarity, he said, is particularly needed on notified body designation; implementing acts; duration of certificates; and on when

the databases will be ready and registration will be possible.

When it comes to clinical evaluation, Brennan believes that the wording in the regulations is difficult to understand and is "overly complex," as well as "incoherent" in places. More details are needed, for instance, on how to demonstrate equivalence and the practicalities of addressing post-market clinical follow-up and annual reporting requirements.

As for labeling, there are many questions, particularly in terms of timing. Companies do not want to change their labeling now to comply with the regulations, and then have to change it again to reflect compliance with new UDI rules, Brennan stressed.

Brennan also emphasized how "massive" the changes will be for the IVD industry, in particular, under the new regulations.

And he stressed generally how, across the two regulations, "there is a huge amount of work to be done." (See box, "Key Business-Impact Provisions From EU Regs.")

RESOURCE ISSUES

But the most immediately pressing issues for industry, according to Brennan, are questions over whether appropriate resources are available to support this major transition. He said Medtech Europe is ready to apply the necessary resources, but he questions whether all stakeholders are prepared to do the same.

Notified bodies are trying to increase numbers and auditing capacity, he noted. But he is not so sure whether authorities will manage to re-designate all the notified bodies in time, and whether the European Commission will recruit sufficient staff to ensure the system is ready within timelines required by the regulations.

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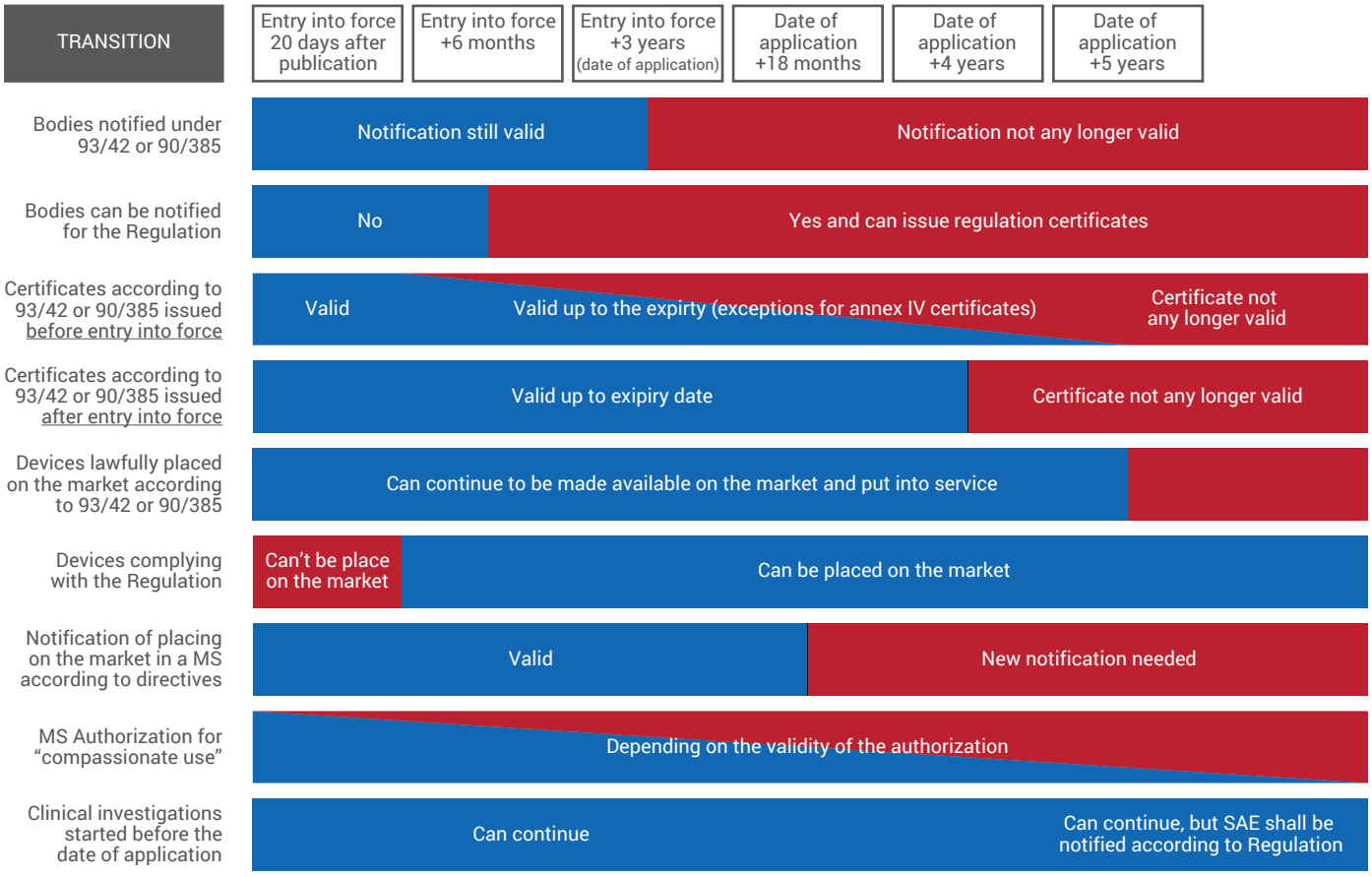
Key Business-Impact Provisions From EU Regs

- High-risk device scrutiny
- Clinical requirements and the new clinical-equivalence approach
- Unique Device Identification and labeling requirements
- New device reprocessing rules
- More frequent notified-body checks
- New fees
- Up-classifications for certain products, such as the move of surgical meshes from class IIb to III
- New registration database
- Validation and training reforms
- Resulting capacity issues with notified bodies

EU implementation timelines



Public Invited To Vet Draft User-Fee Agreement At Nov. 2 Meeting

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Industry and public representatives alike can sign up to participate in an open meeting early next month at US FDA headquarters to talk about the fourth device user-fee deal recently struck with the agency.

FDA and industry trade groups announced that a draft MDUFA IV agreement was reached in August. The agreement includes some new review performance goal categories, upgrades to some existing goals, and a range of structural and process enhancements at the agency. Now, the agency has scheduled a Nov. 2 meeting at its Silver Spring, Md., headquarters for public vetting of the deal, which, if enacted into law, will be the basis for device user fees through fiscal year 2022 after MDUFA III expires on Oct. 1, 2017.

FDA is required by law to hold the public meeting after striking a tentative deal with industry. At the meeting, the agency will take note of public concerns and is also required to open a 30-day comment period for written input.

The agency summarized the deal, previously reported on in *Medtech Insight*, in a Federal Register notice posted Oct. 7. FDA says it will post the full text of a proposed MDUFA IV commitment letter and proposed statutory changes sometime before the Nov. 2 meeting, likely by mid-October. The Federal Register notice sets Nov. 14 as the end of the written comment period (docket No. FDA-2016-24237).

The agency must also by law present the draft recommendations to House Energy and Commerce Committee and the Senate Health, Education, Labor, and Pensions Committee before formally submitting the proposals to Congress.

Industry and FDA negotiated for about a year before reaching agreement, differing for much of the process on the appropriate increase in user-fee collections. Ultimately, the sides agreed on a before-inflation $320.5m increase in the five-year user-fee totals compared to MDUFA III to hire new reviewers while also increasing pay incentives to help the agency compete with the private sector and supporting IT and infrastructure upgrades at FDA. The funds will also support a pilot launch of the National Evaluation System for health Technology, which is an effort to better leverage real-world evidence for medical devices and was a source of some contention during the negotiations.

As part of the draft deal, FDA committed to new performance goals for PMAs, 510(k)s, *de novos*, pre-submissions and other submissions, as well as making improvements to programs, including third-party 510(k) review and digital-health reviews.

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Fees Should Be A Last Resort For NICE Funding, Say UK Medtechs

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The proposal from the UK National Institute for Health and Care Excellence (NICE) to raise fees from its guidance-setting work has drawn a guarded response from the UK medical technology industry association, ABHI.

ABHI voiced it opposition to these fees earlier this week, both on principal and on economic grounds.

The NICE proposal initially extends to technology appraisals (TAs) and highly specialized treatments (HSTs). The fees would be applied in the 2017-2018 financial year. Medtech and the Medical Technologies Evaluation Programme (MTEP) are not expressly mentioned so far, but there is some scope for non-pharma products to be rolled into TA programs where products involving multiple technologies, such as insulin programs, are concerned.

In practice, the TA programs have very little effect on medtech, said ABHI market access director Andrew Davies. But industry already has enough concerns about its cost burden in these current times, and would not welcome NICE fees being extended to the MTEP.

In fact, if NICE did this, the MTEP, under which companies have to submit proposals to NICE to have a technology appraised, would likely suffer. Indeed, the whole program might collapse.

The supposition is that NICE guidance confers a benefit to industry, and that probably *is* the case for pharma. But for medtech to derive similar benefits, payment mechanisms and tariffs would need to be adjusted.

It is not that industry is unsupportive of the HTA body. "We value NICE and its output for the UK and export markets," Davies said, adding that ABHI would not want the see the institute's quality of work suffer.

But fees charged for medtech guidance "should be a last resort," he believes. Nevertheless, ABHI would be prepared to explore other methods of funding with NICE. "We are open to discussions," said

Davies, but stressed that NICE should be mindful of the cost burden already sustained by industry, including the new apprentice levy, and now the extra currency costs that are coming about as a result of UK's Brexit vote.

"Now is not a good time for talk of fees given the current economic landscape or in terms of the role of NICE," Davies said. The activities of NICE might evolve, depending on the content and tone of the yet-to-be-published Accelerated Access Review (AAR).

AAR ON THE CUSP?

Although publication of this long-awaited AAR document is relatively imminent, a firm release date is yet to be ascribed to it. All the Office for Life Sciences has said is that it will be this autumn. ABHI assumes this must mean it will come before next month's autumn statement on the nation's finances, set for Nov. 23.

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German Ambulatory Fast-Track Reimbursement Scheme Failing to Deliver

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Germany's three-year-old scheme for fast-tracking innovative ambulatory medtech products through reimbursement and into circulation is starting to get the doubters talking.

Introduced under an omnibus piece of legislation in 2012, the Erprobungsregelung (Trial Regulation) intended – indeed intends – to allow promising but not sufficiently proven medtech and IVD products to undergo a special route to additional testing, eventually leading to more rapid uptake by the sickness insurance funds.

But the scheme, overseen by the G-BA (Gemeinsamer Bundesausschuss/Joint Federal Committee), has so far failed to promote the rapid passage of innovations into use. At least that was the main takeaway at a recent industry conference in Berlin hosted by German industry association BVMed.

Speaker Professor Thomas Kersting, a senior associate at the IGES-Institut, a private sector policy and research bureau, said the procedure is too involved and bureaucratic to be suited to medtech's rapid innovation cycles. Indeed, no test studies have got underway in the last three years, a situation the G-BA itself describes as "sobering."

The G-BA's Dr. Matthias Perleth said the Trial Regulation (set out in paragraph 137e of Social Law Book V) is a concept for methods, not individual products, and demands proof of benefit through the measurement of patient-relevant endpoints compared to the established standard, and using randomized controlled trials. No studies have been commissioned, often on cost grounds, but consultations with the G-BA are said to be increasing, Perleth told the meeting.

Evidently unimpressed, Kersting voiced his own concerns that similar concepts are not practised in many neighboring European countries, and that the Trial Regulation, together with the new reimbursement evaluation process for class IIb and class III "especially invasive" devices that represent a new clinical pathway will actually slow down access to medtech innovation in Germany.

This high-risk products evaluation process, also overseen by the G-BA, the senior body within Germany's self-governing solidarity system of health-care funding and delivery, was introduced following an amendment to the long-standing NUBs (Neue Untersuchungs- und Behandlungsmethoden – new testing and treatment methods) scheme (paragraph 137h of Social Law Book V).

The NUBs scheme allows a one-year pass through for innovative devices that are not yet part of a Diagnosis Related Group (DRG). But Kersting said that NUBs currently represent just 0.2% of hospital spending (€110m – $123m) and barely 40,000 out of 19 million procedures carried out annually in Germany.

Perleth conceded that the NUBs application process, which individual hospitals must oversee, are complex. He voiced a preference for each single method to be tested in a single study and to be made available to all users. But the discussion left BVMed chairman Meinrad Lugan questioning how start-ups can be expected to navigate these systems at all, and whether Germany really is serious about adopting medtech innovation at pace.

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BREXIT Q&A:

Where Do Notified Body, Authorized Representative Offices Need To Be?

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John Adcock

What regulations will medical device businesses have to follow after the UK exits the EU – the existing EU Medical Device Directives, next year's new EU Medical Device Regulation and the MEDDEV associated guidance, or something new? And what avenues will there be to trade with the EU, and for the EU to trade with the UK? These are among the questions that are facing all device manufacturers and distributors that are either based in the UK, or are selling into the UK and EU.

John Adcock is managing director at Advena, a UK-based consultancy specializing in authorized representative services. Firms like his need to support not only UK-based industries as a result of Brexit, but they also must consider the future situation for firms exporting into the UK and the EU.

Provided that effective government pressure can be applied to assure some form of reciprocal medical device trade with EU countries, it could work out satisfactorily, Adcock said. But that does not lessen the current uncertainty surrounding the role and status of some of the key economic operators with whom manufacturers must interact, such as notified bodies, authorized representatives, and even their EU importers and distributors, he noted.

Medtech Insight invited Adcock to explain his views and why his UK-based consultancy has recently set up an office in Malta – a critical choice in the light of the pending Brexit.

Medtech Insight: What will the UK's role be in shaping device regulation in the post-Brexit future?

John Adcock: If we leave the EU, the good news is that it may be possible for the UK's Medicines and Healthcare products Regulatory Agency to still have some global influence to support device regulation internationally.

But there is concern about how the UK could assure that its own medical device industry is able to compete in the EU if they have no say-so on inherited EU regulation. The MHRA is certainly making the point that it is a key EU medical device player with respect of the up-and-coming regulatory changes, but the political climate in the EU could still push them to one side. There may be no appetite in Brussels to have the UK try to tweak regulations to suit themselves if they are not members of the "club."

What will happen to notified bodies in the future, in your view?

Adcock: That is a good question. We don't know at this point because it depends on the agreement that the UK reaches with the EU. But if there is no straightforward recognition in the EU of UK notified bodies, issues that will arise will include whether the notified bodies will all need dual – or alternative – EU addresses, and need to be accredited from new EU addresses. Otherwise, it seems likely that companies will have to change notified bodies.

We know that BSI and other major UK notified bodies, are not, apparently, concerned as they have bases in other EU counties and could operate their certification business from these alternative sites, but how much influence they will have in standards-making for any new state-of-the art medical devices is a big unknown.

Indeed, when it comes to standards, there is a question over what standards the UK insist on for products to be sold in the UK? And will European standards still be used even though BSI may have no further influence on amendments?

What about the future for authorized representatives?

Adcock: Authorized representatives, and indeed all consultants, must be ready to lead and work with both the national and international medical device industry now to assure they support their clients, whatever the UK and EU politicians throw at them.

Certainly we have found that the Brexit news is now out internationally and many new clients are showing concern about locking into using authorized representatives who have their "registered place of business" in the UK and depend on UK MHRA registration processes.

Other questions include whether medical device manufacturers from the UK will need authorized representatives to sell in the remaining EU countries. Also, whether the UK will set up its own requirements for authorized representatives so manufacturers from outside the EU may need two authorized representative names and addresses, one for the UK and the other for the EU.

Whatever happens, the UK-located consultants will have to compete with the major EU consultants who offer EU-based authorised representative services and EU local registrations.

What about the need to have a base in an English-speaking country for North American clients, for example?

> "If there is no straightforward recognition in the EU of UK notified bodies, issues that will arise will include whether the notified bodies will all need dual – or alternative – EU addresses, and need to be accredited from new EU addresses."

Adcock: Authorized representatives, and other consultants, particularly those working with North American manufacturers and in other major English-speaking international locations, may need to still be based in prominently English-speaking countries so as to offer an assured service. Non-EU manufacturers will certainly feel more comfortable with that scenario, especially if they have been working with UK consultants for many years.

This is another reason why they may need to offer authorized representative services from two locations, the UK and the EU if they are to ensure continuity of service.

All these factors could lead to there being more consultancy companies with two or more registered places of business.

What has the response been at your company in terms of its role as an authorized representative, and would you recommend this to other authorized representatives?

Adcock: After extensive research, Advena has set up a subsidiary office in Malta for EU registrations. In Malta the company is still "Advena Ltd.," and only the address is different. This could be particularly comforting for clients who may need to change their labeling in the future.

Others may follow, but there are not too many English-speaking EU countries like Malta with cost-effective registration systems [and] few bureaucratic hurdles.

So, in light of these uncertainties, what would you advice industry to do?

Adcock: Medical device manufacturers and their contracted authorized representatives must practically and efficiently work through any political eventuality that Brexit is throwing at them. It is no good despairing – although very tempting for some – but there are opportunities that could start to be worked on now that we have some form of timetable.

Of course, we still don't know how the regulations will pan out and what regulations the UK will adopt, so the unknown will be there for some time – it may take months or even years to get the full facts. However, the option to do nothing, and not to plan ahead for all eventualities, would not be a wise business decision.

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Singapore Brings Southeast Asia Into IMDRF Fold

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Singapore has become a member of the International Medical Device Regulators Forum, raising hopes for even more convergence of device regulations in south-east Asia and in other international markets in general.

The country is the first Southeast Asian nation to become a member of the IMDRF's management committee, whose other members are Australia, Brazil, Canada, China, the EU, Japan, Russia and the US.

It is already an active member of the Asian Harmonization Working Party and the Association of Southeast Asian Nations. As such, the country's acceptance in the IMDRF is expected to promote mutual understanding among the various harmonization initiatives and help leverage expertise, according to Jack Wong, founder and secretary general of the Asia Regulatory Professional Association.

Singapore was an early pioneer of the AHWP in the 1990s, and since then it has continued to play a key role through various leadership positons, said Tran Quan, VP of regulatory affairs at the Asia Pacific Medical Technology Association (APACMed).

"As the first ASEAN country in the IMDRF management committee, Singapore will no doubt further enhance the ongoing collaborative effort with AHWP to achieve regulatory convergence in the region," Quan told *Medtech Insight*.

Quan believes that Singapore can also help ensure the smooth implementation of the ASEAN Medical Device Directive (AMDD) by sharing best practices from its participation in IMDRF with the 10 ASEAN economic members that have pledged to adopt and implement the AMDD in their respective jurisdictions.

Wong told *Medtech Insight* that the AMDD's implementation "needs a lot of training and experience [and] coaching." He said medtech regulatory experts at the IMDRF can add great value to this work and that "it is great news" to have more Asian representation within IMDRF.

Singapore was unanimously accepted as a member of the IMDRF's management committee at the organization's 10th meeting that took place in Florianópolis, Brazil, from Sept. 13-15.

An IMDRF statement on why it accepted Singapore's request

for membership explained that the country had been engaged in forum's activities and demonstrated its capacity of contribution. Other membership requirements that Singapore fulfilled included that it had:

- A mature or maturing system for medical device regulation;
- A recognized commitment to the objectives of IMDRF;
- A capacity to contribute resources and expertise to the objectives of IMDRF; and
- Regional influence.

Separately, APACMed is planning to host a regulatory panel at its annual Asia Pacific MedTech Forum 2016 in Singapore in November that will explore what has been achieved with regard to harmonization and consider how to move forward. "Following this, we will host our first full-day MedTech Regulatory Affairs Meeting to address the complexities and challenges of the regional regulatory environment," said Quan. "This includes a workshop to examine how capacity building can be applied to Asia Pacific's rapidly changing landscape from the perspective of regulators and industry, where the outputs will be developed into a white paper."

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WHO Plans New Fees For IVD Prequalification In Early 2018

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New financing arrangements for the prequalification of *in vitro* diagnostics by the World Health Organization are expected to come into effect in early 2018 as part of a wider initiative to broaden the scope of the prequalification program.

IVDs will be subject to a new fee framework, similar to the fee-for-service model that WHO announced it will apply to medicines and vaccines from January 2017. Under this new structure, manufacturers are expected to contribute some $20m per year to the vaccines and drug program – equivalent to half of its operating costs – in the form of fees. The aim is to take the burden off donors like the Bill & Melinda Gates Foundation and UNITAID and allow the program to be sustained and expanded.

It's not clear exactly why IVD manufacturer fees are not being addressed at the same time as those for drugs and vaccines, although it could be because they have different lifecycles, and so it is necessary to work out how to adapt the proposed fees to their particular needs.

Sue Hill, director of Essential Medicines and Health Products at WHO, said that the organization held discussions with diagnostics manufacturers, but that because the prequalification program on diagnostics was less well developed than that for medicines and vaccines, "their fees will need to be reviewed next year as we also review the scope of that program."

WHO has undertaken other initiatives this year in relation to prequalification of IVDs. For example, it is planning to adopt a faster process for verifying the performance of IVDs submitted under the program, the intention being to shorten assessment and decision times.

And in February this year, the organization issued draft guidance explaining the changes to prequalified IVDs that manufacturers must report to the WHO. It warned that failure to report changes in accordance with the requirements set out in the document could result in the delisting of the product from WHO's list of prequalified IVDs.

BACKGROUND TO IVD PREQUALIFICATION

The IVD prequalification program is intended to promote and facilitate access to safe, appropriate, affordable and good quality IVDs in an equitable manner, with the focus on products for priority diseases and their suitability for use in resource-limited settings, WHO says.

It includes three components: review of a product dossier; laboratory evaluation of performance and operational characteristics; and manufacturing site inspection. The findings of the IVD prequalification program are used to provide independent technical information on safety, quality and performance of IVDs, principally to other UN agencies, but also to WHO member states and other interested organizations to guide their procurement practices.

The overall prequalification program covers an average of 80 medical products a year: to date, WHO says it has prequalified 516 medicines, 180 vaccines and 64 IVD tests.

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VC DEALS ANALYSIS:

One Big Beat After Long Lull

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Venture funding levels in 2016 could still be in the running to beat the previous year's performance after September saw the return of the big-buck financing round.

Medtech Insight's VC deal tracker recorded 22 transactions in September, just one more than in the previous month. But while most of August's deals were in the low-dollar range, September bagged a $215m round by drug delivery company Intarcia Therapeutics. (*See Figure 1*). This is the first nine-figure deal since April and has helped to narrow the deal value gap that opened up at the end of August.

The Intarcia financing is only the first tranche of what it hopes would be a larger $600m round. The Boston firm counts several well-known health-care VCs like New Enterprise Associates, Venrock and New Leaf Venture Partners among its investors, and it will be using the funds to take its first product – a subcutaneous matchstick-sized implant that continuously delivers exenatide for controlling type 2 diabetes – through to US regulatory approval and market launch.

This deal significantly bumped up the total takings in September to nearly $570m, more than double that of August's $253m and even beat the $522m recorded a year ago. September 2015 had also benefited from an exceptionally large transaction, but the $150m round raised by stealth mode Auris Surgical Robotics was no match for Intarcia's $215m. Indeed, this September's performance is the best in the past four years. (*See Figure 2*).

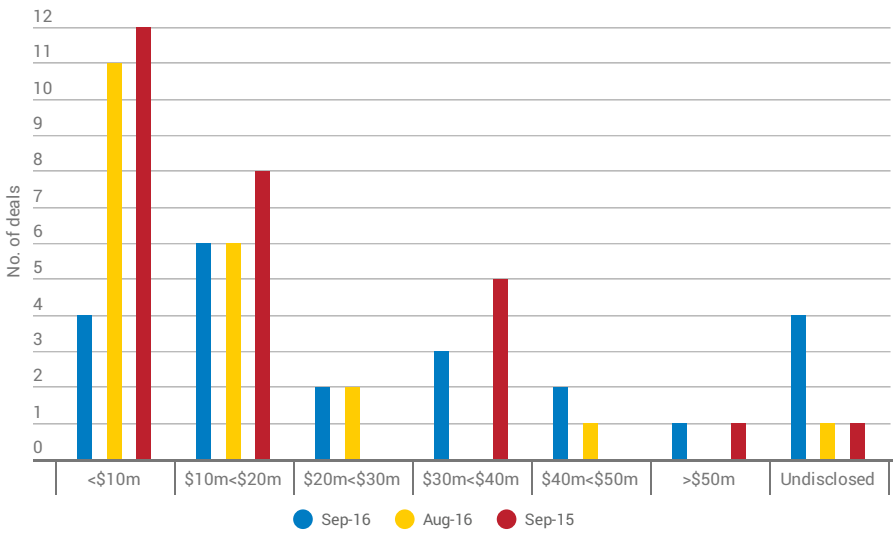
The four-month hiatus between April and August left 2016 deal value levels trailing behind 2015's and even with the boost from September, the total takings for the first nine months of 2016 has only just exceeded $3.90bn, slightly behind the $3.94bn

CLICK

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

FIGURE 1

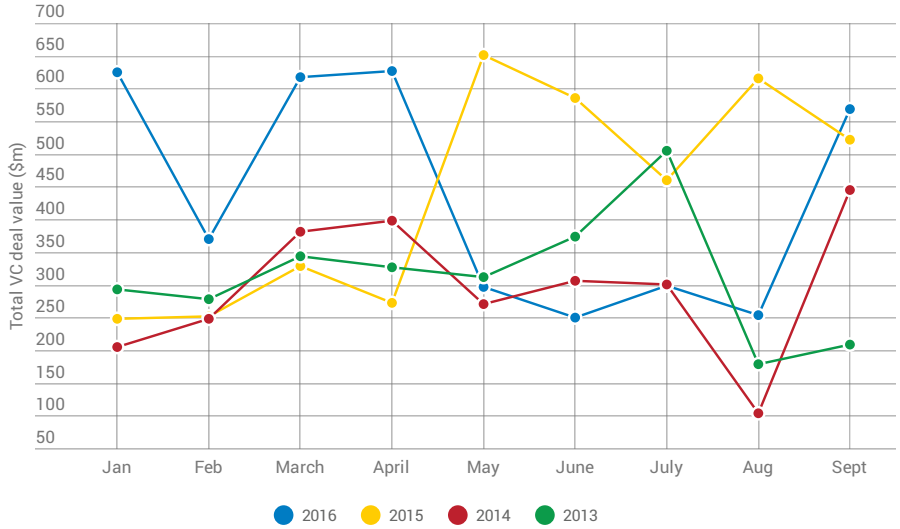
No. of deals by amount raised (Sept. 2016 vs Aug. 2016 vs Sept. 2015)



Source: Medtech Insight's VC deal tracker

FIGURE 2

Total amount raised by month, Jan.-Sept. 2013-2016



Source: Medtech Insight's VC deal tracker

	SEP 2016	SEP 2015	SEP 2014	SEP 2013
Total VC deal value* ($m)	569.8	521.8	446.0	209.4

**Including only deals that disclosed financial details*

Top VC deals in September 2016, by amount raised

RANKING	COMPANY	BASED IN	PRODUCT/ THERAPY SECTOR	AMOUNT RAISED	FINANCING ROUND	TOTAL INVESTMENT
1	Intarcia Therapeutics	MA, US	Drug delivery	$215m	Undisclosed	Undisclosed
2	Chrono Therapeutics	CA, US	Drug delivery/ Digital health	$47.6m	Series B	$79.6m
3	Color Genomics	CA, US	IVD	$45m	Series B	$60m
4	Rox Medical	CA, US	Vascular	$40m	Series E	$46m
5	SentreHeart	CA, US	Surgery	$35m	Series D	Undisclosed

Source: Medtech Insight

recorded in the same period last year.

That said, Intarcia is expecting to close its second larger tranche of financing in the fourth quarter this year. If the company succeeds in pulling this off in this timeframe, we should see at least one more nine-figure deal in the next three months that would definitely put 2016 ahead of 2015.

SOME MEATY DEALS

Aside from Intarcia, September saw some other meaty transactions in the higher dollar range of $35m and above. (See table below). These came from a range of product sectors, and included Chrono Therapeutics which combines drug delivery with another hot sector in medtech investment circles: digital health.

Chrono – which grabbed the second largest deal, raising $47.6m in Series B funds – has developed a digital-health solution to help smokers kick the habit. Its product includes a wearable device that communicates with a mobile app via Bluetooth and delivers nicotine to the patient transdermally.

Drug delivery, together with orthopedics, were the second most popular product sector for investors in September, while IVD and Cardiology/Vascular came joint first. (*See Figure 3*).

Looking at which are the hot investment spots this year to date, IVD and cardiology continue to be favorites, but with investors spreading their bets on an increasingly diverse range of product/therapy areas, there may be some surprises in store at the end of the year.

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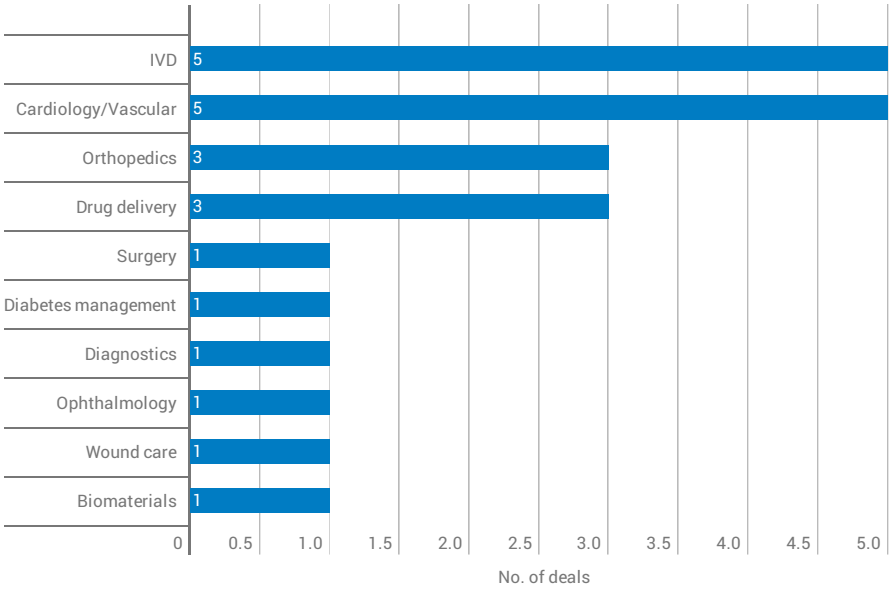
FIGURE 3

No. of deals by product/therapy sector



Source: Medtech Insight's VC deal tracker

M&A DEALS ANALYSIS:

Big Bucks Are Back

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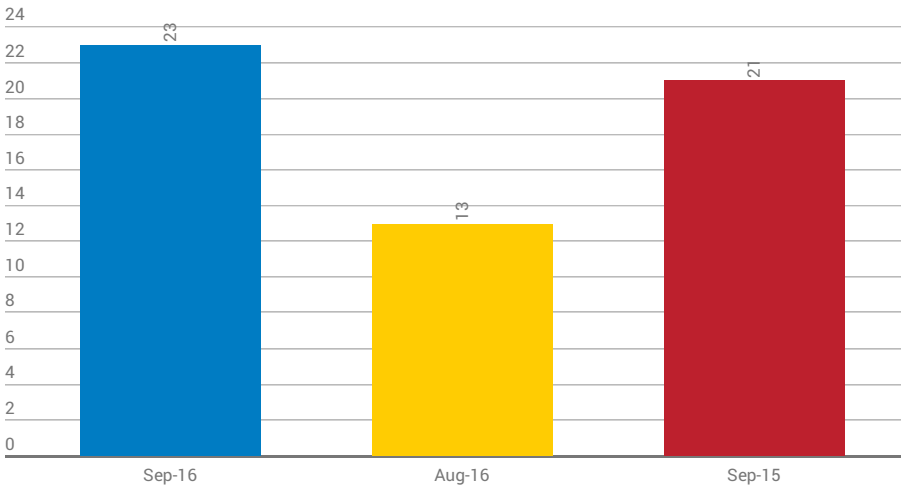
September was the busiest month so far in 2016 for M&A deals with activity picking up following a summer slump. *Medtech Insight's* M&A deal tracker recorded 23 transactions in total, a significant jump from the 13 seen in August (*See Figure 1*). Deal volume was also slightly higher year-over-year, with 21 M&A deals recorded in September 2015.

The deals in September were represented by 14 different product sectors, with IVD leading the way with four deals and three deals each in imaging and orthopedics (*See Figure 2*).

FIGURE 1

No. of M&A deals, Sept. 2016 vs Aug 2016. vs Sept. 2015



Source: Medtech Insight

BIG BUCKS ARE BACK

The summer months had been particularly slow for M&A activity, not only in terms of deal volume but also in the notable absence of big-buck transactions. In the 13 deals recorded in August and the 10 in July, there were no acquisitions valued at more than $500m.

However, September saw two major deals closing at $4bn and above. **Danaher Corp.** offered to pay $53 per share to acquire molecular diagnostics company **Cepheid** in a deal valued at $4bn, and **Johnson & Johnson** acquired Abbott's ophthalmic surgical business **Abbott Medical Optics Inc.** (AMO) for $4.33bn.

Cepheid develops molecular systems and tests, including GeneXpert genetic testing. *GeneXpert* systems enable rapid, genetic testing and provide test results for infectious diseases. Cepheid will become part of Danaher's $5bn diagnostics segment, joining the company's Beckman Coulter, Leica Biosystems and Radiometer businesses.

Based on its public disclosures, Cepheid generated annual revenues of $539m in 2015, and Cepheid disclosed that in 2016 it expects to generate $618-635m in revenues.

The top deal of the month was the announcement that **Johnson & Johnson** would acquire **Abbott Medical Optics Inc.** (AMO), for $4.33bn in cash. The deal adds a surgical component to J&J's business, which currently consists of contact lenses and solutions.

> The top deal of the month was J&J's acquisition of Abbott Medical Optics for $4.33bn in cash.

Another significant deal in September was **Boston Scientific Corp.**'s proposed purchase of **EndoChoice Holdings Inc.**, a specialist in gastrointestinal endoscopy products and services; the deal will expand Boston Scientific's endoscopy portfolio. Under the terms of the agreement, Boston Scientific will pay $8 in cash per EndoChoice share, giving the deal a total enterprise value of $210m.

The list of medtech deals for September 2016 includes 17 for which the financial terms were not disclosed. Among this was **Nestle SA**'s staged acquisition of **Phagenesis Ltd.**, a UK medical device company working on a new treatment for dysphagia, a condition where patients have lost the ability to swallow.

Under the terms of the agreement, Nestle will make an upfront payment of an undisclosed amount, followed

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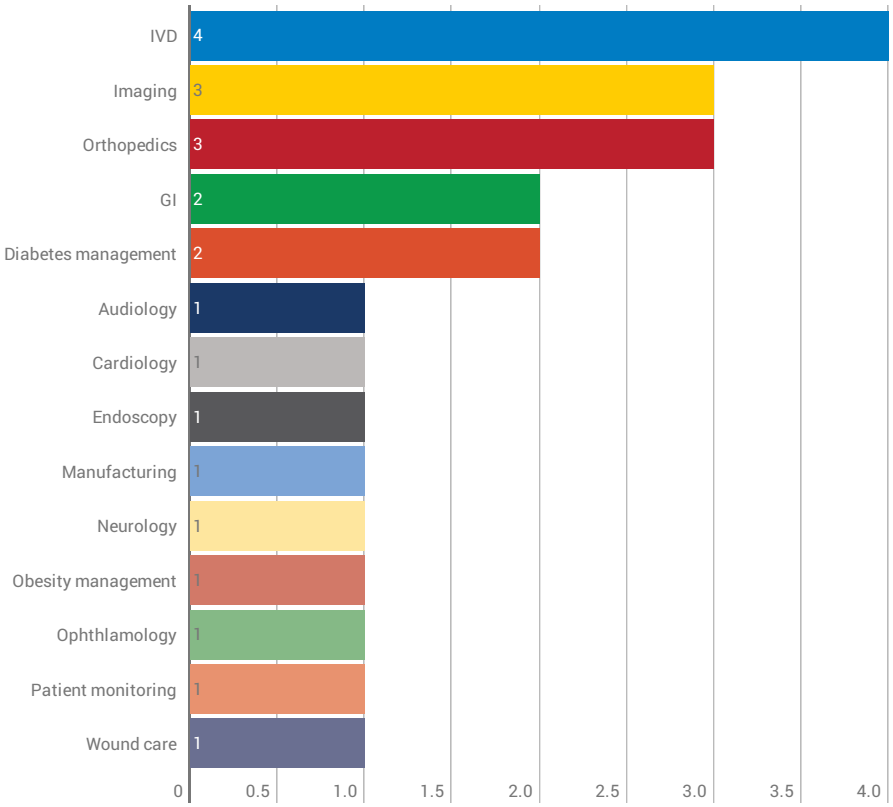
For more details about M&A deals, go to Medtech Insight's M&A deal tracker: https://medtech.pharmamedtechbi.com/datasets/mna

FIGURE 2

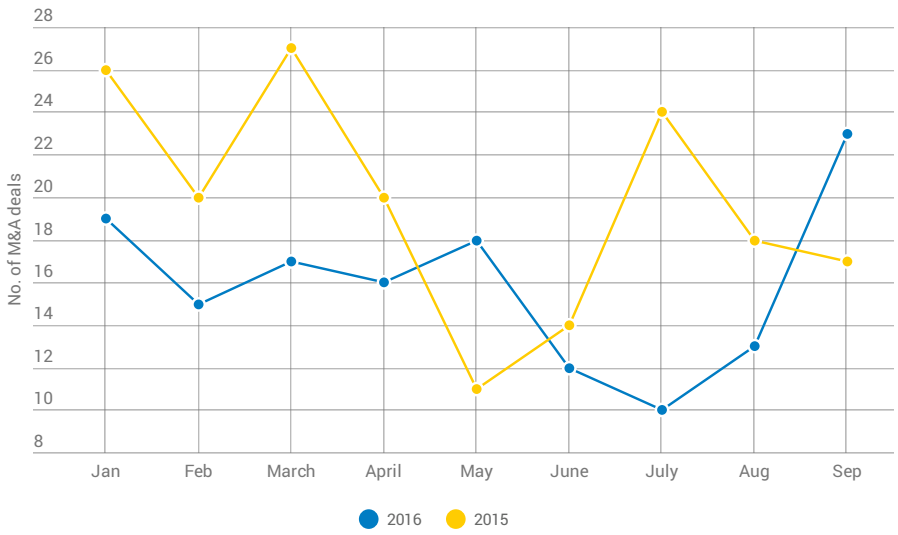
M&A deals by product sector, September 2016



Source: ***Medtech Insight***

FIGURE 3

No. of M&A deals, Jan.-Sept. 2016 vs 2015



Source: Medtech Insight

by additional funding based on the achievement of certain milestones as Phagenesis completes the clinical evaluation of its Phagenyx device. Phagenyx uses Phargyngeal Electrical Stimulation (PES) to treat the neurological cause of dysphagia.

The staged acquisition will be based upon successful completion of European and US development programs anticipated by 2019. The deal is the latest acquisition by Nestle in the medical sector. The CEO of Nestle Health Science (NHSc), the subsidiary of Nestle into which Phagenyx will be integrated, said dysphagia was a "strategic" focus for the company; NHSc already sells a number of special nutritional solutions for dysphagia patients.

The most acquisitive company in 2016 so far is Stryker, which carried out its 7th and 8th acquisition of the year in September. The company announced it has acquired Ivy Sports Medicine and Instratek for undisclosed sums. Former acquisitions carried out by Stryker in 2016 include Sage, Valenat, Physio-Control International, SafeWire, Becton Dickinson and Stanmore. Stryker is currently leading the way with eight acquisitions in 2016, with last year's most prolific shopper Medtronic trailing behind with five.

ACTIVITY YTD

At the end of September, there have been 143 M&A deals in 2016. This is down from the 177 deals announced for the same period in 2015. (See Figure 3).

A breakdown of deals by quarters show a drop in volume, compared to 2015. Only the second quarter of 2016 had more deals compared to Q2 2015, but only by one.

In 2016 so far, each month has averaged 15-16 M&A deals. If the deal flow continues at the same rate, this would put the year on track for about 180-192 deals, falling short of the 237 recorded in 2015 or the 269 recorded in 2014.

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STARTS & STOPS:

Medtronic's Symplicity Flatlines For Heart Failure

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Symplicity-HF, the study of **Medtronic PLC** 's catheter-based renal denervation technology in patients with chronic heart failure and renal impairment, is among four trials that were terminated in the last month.

The approved indication for renal denervation technologies, including *Symplicity*, is for controlling treatment-resistant hypertension, but there has been some evidence suggesting that renal denervation could have a therapeutic effect on arrhythmias which often occur in chronic heart-failure patients. In February 2012, Medtronic initiated the Symplicity-HF trial in Australia and Europe, primarily to assess the safety of renal denervation, as measured by adverse events, in patients with NYHA Class II or III heart failure and renal impairment with a left ventricular ejection fraction of less than 40%. The secondary endpoints of the trial looked at ventricular function, as a measured by echocardiography, and renal function, as measured by glomerular filtration rate. The study enrolled 39 patients in total and the primary completion date was June 2015.

In October 2015, at the American Heart Association annual meeting, Medtronic presented the primary results of Simplicity-HF. A 12-month follow up of the 39 patients enrolled showed no significant adverse events related to the renal denervation procedure and the one death recorded was related to cardiovascular issues. However, the data showed that there was "no clinically meaningful changes in indices of cardiac or renal function" following renal denervation. So while it looks like Symplicity met its primary endpoint, Medtronic's technology was not able to provide evidence that renal denervation could be beneficial to heart-failure patients.

Following the AHA presentation, Medtronic continued to follow up the patients for an additional year, as per the DSMB recommendation, and then decided to terminate the study as was noted in the Oct. 4 update on clinicaltrials.gov.

This is not the first knockback suffered by Symplicity; in 2014 Medtronic was blindsided by the failure of a pivotal trial, Symplicity-HTN3, in which renal denervation with Symplicity did not show any benefit in treating refractive hypertension. However, Medtronic and other renal denervation players have managed to pick up the pieces with a rethink of the trial design, and this space is once again seeing some cautious optimism. With this lesson in mind, renal denervation for heart failure may not be a completely lost cause, and a trial redesign could produce different outcomes.

When asked about what could have contributed to renal denervation showing "no apparent efficacy" in helping heart failure patients, a Medtronic spokesperson commented: "A key factor was that Symplicity-HF employed the same device and similar procedural techniques as the Simplicity-HTN3 trial. Indeed, sub-analysis of data from a small cohort of Symplicity-HF patients of 'renal norepinephrine spillover', an established index of renal sympathetic activity, indicated wide variability in the actual level of denervation achieved. Therefore, the neutral results of the [Symplicity-HF] trial do not disprove (or prove) the hypothesis that heart failure patients might benefit from renal denervation."

Medtronic is hoping that the ongoing REACH trial – a prospective randomized double blinded, sham controlled study of over 60 patients with systolic heart failure, sponsored and executed by Prof Justin Davies at the Imperial College London, and using Medtronic's new Spyral and G3 generator technology – might throw more light. "Results [from REACH] may be reported within the next 9-12 months. Due to its more rigorous design and the application of next-generation technology, we expect this trial to add key new insight into the potential of renal denervation therapy to improve heart failure," she told *Medtech Insight*.

Aside from Symplicity-HF, two other cardiology-related trials were terminated in September.

Heart stent-maker **OrbusNeich** initiated in July 2013 a non-randomized, prospective, multicenter registry without a comparison group to collect and process historical data of implantations with the *Combo* dual therapy stent in Germany. The DTS registry was expected to enroll a thousand patients, but as of Sept. 30 it enrolled only 130 patients.

Abbott Laboratories Inc. has terminated its 12-center, European post-marketing clinical trial of *MitraClip*, comparing the performance of the percutaneous mitral valve repair system against surgical therapy in patients with intermediate-to-severe degenerative mitral regurgitation. The trial was initiated in April 2015 and it was planned to complete in September 2018. When the trial was terminated last month, there had not been any patients enrolled. No reasons were cited for the trial termination.

Finally, **Philips** cut short its Phase II/II clinical study of the Philips *Sonalleve* magnetic resonance-guided high intensity focused ultrasound system. The study was to assess the system's efficacy in the treating symptomatic uterine leiomyomas (uterine fibroids); it was initiated in June 2012, with a view to completing by March 2016 and having 224 patients enrolled. Only 49 patients were enrolled as of September and it was noted that "it was not possible to enroll patients into the study in a realistic timeframe."

The table below details other medtech trial initiations and completions in the last month, as recorded by Informa's Meddevicetracker.

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Trial starts and stops – Sept. 8-Oct. 7, 2016

DATE	COMPANY	PRODUCT NAME	TRIAL NAME	COMMENTS
TRIALS INITIATED				
Sept. 28	Edwards Lifesciences Corp. (EW)	FORMA for Cardiac Valve Surgery	SPACER (EU & CAN)	A study to assess the safety and device performance of the Tricuspid transcatheter repair system in patients with clinically significant, symptomatic, tricuspid regurgitation who are at high surgical risk for standard tricuspid repair/replacement. It expects to enroll 75 patients.
Sept. 18	MitraSpan, Inc.	MitraSpan Device for Cardiac Valve Surgery	SPARE-MR (EU)	A human feasibility study of the MitraSpan device (SPARE-MR). The inclusion criteria include moderate-severe, symptomatic, secondary mitral regurgitation with left ventricular ejection fraction 20-50%.
Sept. 15	Edwards Lifesciences Corp. (EW)	SAPIEN 3 for Cardiac Valve Surgery	TAVR UNLOAD (US, CAN, EU)	An investigator-initiated study to determine the safety and efficacy of transcatheter aortic valve replacement with SAPIEN 3 via a transfemoral approach in heart failure patients with moderate aortic stenosis as compared with optimal heart failure therapy. The study expects to enroll 600 patients.
Sept. 13	Insulet Corporation (PODD)	Omnipod Horizon System for Diabetes Mellitus, Type I	Omnipod Horizon feasibility study (US)	The first patient has been enrolled in Insulet's feasibility study of its Omnipod Horizon automated glucose control system). The full study will evaluate the use of a personal Model Predictive Control algorithm with the Omnipod platform in 20 adults with type I diabetes and is taking place in a clinical research center setting to gather data to be used to evolve the algorithm in subsequent studies leading to US FDA submission.
Sept. 12	Preceyes B.V.	PRECEYES Surgical System for Other Ophthalmological Indications (Ophthalmology)	Clinical trial of PRECEYES robotic-assisted surgical system for ocular surgery (UK)	A clinical trial sponsored by the University of Oxford to assess Preceyes' robotic system for performing new gene therapy operations, which are currently under development and require ultra-precise surgery under the fovea.
Sept. 12	Orthofix International N.V. (OFIX)	Physio-Stim for Bone Fractures and Mechanical Defects	Physio-Stim for Osteoarthritis of the Knee (US)	A study evaluating the use of pulsed electromagnetic field (PEMF) technology for osteoarthritis of the knee. It will assess the efficacy and safety of Orthofix's Physio-Stim system in reducing inflammation and restoring homeostasis of the extracellular matrix, potentially providing symptomatic relief of OA pain, reducing cartilage breakdown and stimulating new cartilage formation. It expects to enroll 150 patients.
Sept. 7	EyeSense GmbH	Continuous Glucose Monitoring System for Diabetes Mellitus, Type II	Phase I clinical study for a continuous blood glucose monitoring system (Hong Kong)	A clinical study, conducted as a collaboration between the Chinese University of Hong Kong, EyeSense, and Powder Pharmaceuticals to assess EyeSense's CGM device based on a novel optical sensing technology. It expects to enroll 10 patients.
TRIALS SUSPENDED				
Oct. 4	Medtronic plc (MDT)	Symplicity Renal Denervation System for Hypertension (Systemic)	Phase IV - SYMPLICITY-HF (EU/Australia)	A feasibility study in Australia and Europe to demonstrate the renal denervation with the Symplicity Catheter is safe and determine the evidence of a response to renal denervation in patients with heart failure has been terminated due to "no apparent efficacy," although there were no significant safety issues. The study enrolled 39 patients out of the anticipated 40.
Sept. 29	OrbusNeich	COMBO Dual Therapy Stent for Coronary Artery Disease	DTS Register (Germany)	A non-randomized, prospective, multicenter registry without a comparison group to collect and process historical data of implantations with the COMBO Dual Therapy Stent in Germany has been terminated due to low enrollment. The study was initiated in 2013 and anticipated enrolling a thousand patients; it enrolled 130 patients at the end of September 2016.

DATE	COMPANY	PRODUCT NAME	TRIAL NAME	COMMENTS
Sept. 28	Koninklijke Philips N.V. (PHG)	Sonalleve MR-HIFU for Uterine Fibroids	Phase II/III - (SOFIA)	A Phase II/II clinical study (SOFIA) to determine whether treatment with the Philips Sonalleve Magnetic Resonance-guided High Intensity Focused Ultrasound (MR-HIFU) system is effective in the treatment symptomatic uterine leiomyomas (uterine fibroids) has been terminated because it was not possible to enroll patients into the study in a realistic timeframe. The study had enrolled 49 patients.
Sept. 8	Abbott Laboratories (ABT)	MitraClip for Cardiac Valve Surgery	Phase IV - HiRiDe (University of Zurich)	A Phase IV study comparing MitraClip to Surgical therapy in high and intermediate risk patients (HiRiDe Study) has been terminated. No reason was given for terminating the trial.
TRIALS COMPLETED				
Oct. 4	ReWalk Robotics (RWLK)	ReWalk for Paralysis	RW003 ver. 4 (US)	A 32-patient study investigating the safety and performance evaluation of ReWalk reciprocating gait orthosis.
Sept. 25	BIOTRONIK AG	Pantera Lux for Coronary Artery Disease	BIOLUX-RCT (EU)	A randomized controlled trial comparing the clinical efficacy of Pantera Lux paclitaxel-releasing balloon against the drug-eluting Orsiro hybrid stent system in patients with in-stent restenosis. The study enrolled 231 patients.
Sept. 18	Medtronic plc (MDT)	Reclaim DBS Therapy for Obsessive-Compulsive Disorder	Phase IV - OCD PMCF (Europe)	Phase IV study to monitor the safety and performance of Reclaim Deep Brain Stimulation (DBS) Therapy in patients with chronic, severe, treatment-resistant obsessive compulsive disorder. The study enrolled 32 patients out of the anticipated 36.

Source: Meddevicetracker

US APPROVALS ANALYSIS:

Strong Q3 For Metabolic-Disease Devices

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Products addressing metabolic conditions attracted the most attention from US FDA's novel device approval pathways in September.

Of the five original PMAs approved last month by the agency, two target diabetes and one targets obesity. In addition, FDA granted a *de novo* classification to another obesity device – one of three *de novos* in September.

Overall, the agency had a productive September in approving and clearing devices, hitting totals above 2016 averages for all main submission types. And the third quarter was FDA's most productive period of calendar year 2016 for original PMA and PMA supplement approvals, as well as 510(k) clearances, according to *Medtech Insight*'s Approvals Tracker.

Among the devices that made it through the most demanding FDA pathway – original PMA – was **Obalon Therapeutics Inc.'s** *Obalon* intragastric balloon, which was approved Sept. 8 for obese individuals with a body mass index of 30 kg/m^2 to 40 kg/m^2 who have failed to lose weight through diet and exercise. It will compete directly with two intragastric balloons approved last year – **ReShape Medical Inc.**'s *ReShape* balloon and **Apollo Endosurgery Inc.**'s *Orbera*. It will also go up against other recently approved, minimally invasive obesity systems.

But the most highly anticipated approval that came through in September was likely for **Medtronic PLC**'s *Minimed 670G* closed-loop insulin pump-continuous glucose monitor system, dubbed an "artificial pancreas." That historic approval followed soon after the agency's go-ahead for **Abbott Laboratories Inc.'s** *Freestyle Libre Pro* flash glucose-monitoring system.

There was also one original PMA approval for an oncology companion diagnostic – another win for **Roche**'s *cobas EGFR Mutation Test v2* assay, and another in ophthalmics, for **Carl Zeiss Meditec AG**'s *Visumax* femtosecond laser.

The *de novo classification process* has also been an increasingly popular pathway to bring completely novel devices to market if they can be shown to be moderate-risk rather than high-risk. Among the three *de novo* classifications in September, the agency granted market access to **Scientific Intake Ltd.**'s *Sensor Monitored Alimentary Restriction Therapy* (SMART) device on Sept. 26. SMART is a sensor-embedded custom-made oral

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For sortable and searchable tables of all 2016 US and non-US approvals and clearances, check out our Approvals Tracker.

device that is placed in the mouth only while eating to force smaller bites, require chewing and other adjustments to eating habits intended to reduce weight, and also to track weight-loss goals.

FDA also granted *de novo* clearance to **Johnson & Johnson**'s *Acclarent Aera* ear, nose and throat dilation system for treating eustachian tube dysfunction, and **Stryker Corp.**'s *Trevo ProVue* and *XP ProVue* as a first-line therapy for ischemic stroke.

APPROVALS, CLEARANCES UP IN THIRD QUARTER

De novo submission activity has been picking up since fiscal year 2013 when the law was changed to allow companies to access the pathway for moderate-risk devices without first needing to unsuccessfully pursue a 510(k). There have been 17 successful *de novo* classifications in the first three quarters of calendar year 2016, up from 11 in the same period last year (but down slightly from the 20 classifications in September 2014).

There have been 32 original PMAs approved through the third quarter, just shy of the 33 approved at this time in 2015, which was a record-setting year. Meanwhile, FDA is ahead of recent-year performance for panel-track PMA supplement approvals. There were 18 panel-track supplements approved through September of this year, up from 12 and eight such approvals in the first three quarters of 2015 and 2014, respectively.

Approvals of other types of PMA supplements, not including 30-day notices, are also up so far this year, with 660 through September, compared to 576 during the same period last year.

510(k) clearances, the pathway used by most devices to reach the US market, are the only category that remains down in volume this year, with 2,209 clearances so far in 2016 compared to 2,297 in 2015. But the third quarter of 2016 was the most productive quarter for 510(k) clearances so far this year, as it was for PMAs and PMA supplements, as well.

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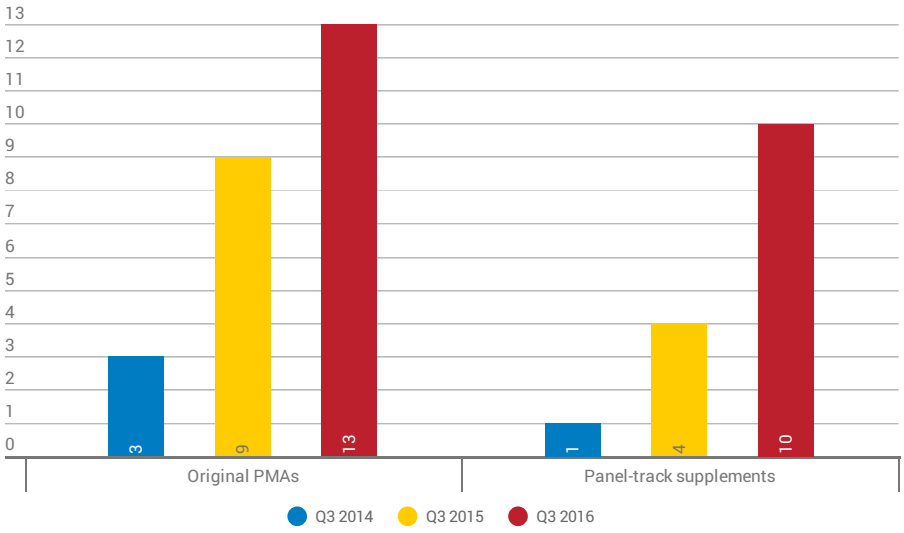
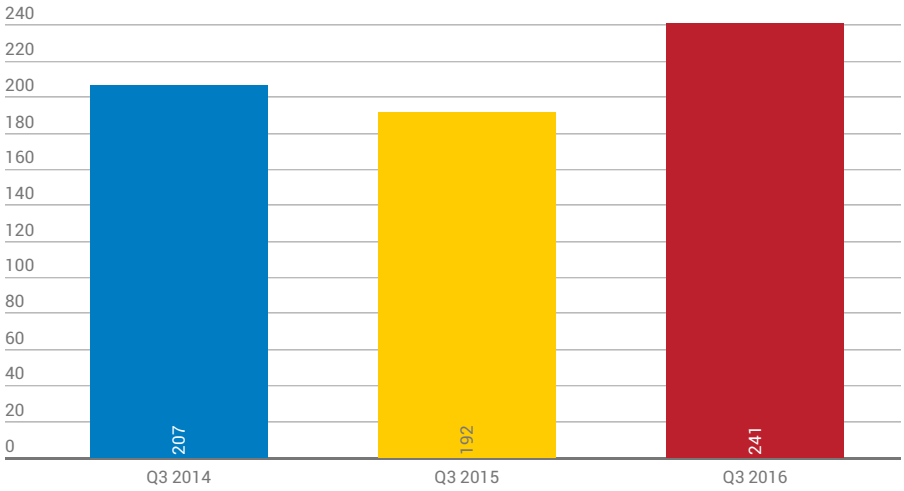
Strong Q3 for PMA approvals, compared to past two years

PMAs and panel-track supplements



Non-panel-track PMA supplements



PMA supplement numbers exclude 30-day notices

Medtech Insight Approvals Tracker

OUS APPROVALS ANALYSIS:

BSX, Edwards Score New CE Marks In TAVR Battlefield; Chinese DES Advances In Asia

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September brought the biggest number of non-US medical device approvals since June, with 16 CE marks and seven approvals in other territories, as tracked by *Medtech Insight*.

The 23 non-US approvals is a big increase over the 17 seen in August and the 18 in July. Coincidentally for this year, September is now the fourth month in 2016 in which the Approvals Tracker recorded exactly 16 CE marks.

Only June, with its outlier figure of 27, had more CE marks in 2016. (*See Figure 1*)

The non-US, non-European territories represented this month include Australia, China, Canada, and Japan, along with Pakistan's first appearance in the Approvals Tracker in 2016.

Devices for cardiovascular indications were the most common category of non-US approvals with five. There were also four in-vitro diagnostic products approved – all in Europe – and four orthopedic devices approved in September outside the US. No other category had more than two approvals.

FIGURE 1

September 2016 Non-US Medical Device Approvals By Territory

MONTH	CE MARKS	OTHER TERRITORIES
Jan	14	7
Feb	16	9
March	16	10
April	14	1
May	16	6
June	27	4
July	13	5
August	12	5
September	16	7
TOTAL	128	47

Source: Medtech Insight

NEXT GENERATION OF TAVR

On Sept. 19, **Boston Scientific Corp.** announced the CE mark-approval of its *Lotus Edge,* the next generation in the company's line of transcatheter aortic valve replacement system. The company says it is better than the earlier version of the Lotus because it is more flexible and its delivery catheter is narrower, which will make it easier to implant in complex anatomy.

Lotus Edge also features *Depth Guard* technology to reduce the need for a permanent pacemaker and minimize paravalvular regurgitation. The need for a permanent pacemaker in many TAVR patients has so-far been one of the potential drawbacks of TAVR in general and the first-generation Lotus especially. For example, in the REPRISE II trial of the first generation Lotus, about 32% of the patients treated with the device needed a pacemaker. At that time, the of pacemaker implantation at one-year ranged from 1.8% to 11.5% with **Edwards Lifesciences Corp.** *Sapien* and *Sapien XT* systems and from 19.1% to 30.3% with **Medtronic PLC**'s *CoreValve.*

Boston Scientific executives have been telling investors for a while that they expect Lotus Edge to be more competitive in Europe with TAVR systems sold by Medtronic and Edwards. The company is still working on bringing a TAVR system to the US market; targeting late-2017 for FDA approval of Lotus based the results of the 1,032-patient REPRISE III IDE study.

Also on Sept. 19, Edwards announced it received a CE mark to expand the indication of its *Sapien 3* TAVR system to include treatment of patients suffering from severe, symptomatic aortic stenosis who are at intermediate risk for open-heart surgery. This indication will make TAVR an option for even more patients who previously would have had to have open-heart surgery, according to Edwards. The company cites a recent propensity score analysis of the SAPIEN 3 observational study by Vinod Thourani of Emory University in Atlanta and colleagues showing that TAVR was associated with significantly superior composite outcomes compared with surgery in intermediate risk patients and therefore may be the preferred treatment for intermediate-risk patients.

Sapien 3 is now approved in Europe and the US for intermediate-risk patients and the company is sponsoring the PARTNER III trial of Sapien 3 in patients with low surgical-risk, suggesting that the company expects TAVR to eventually be available to just about every aortic stenosis patient. But the company has not stopped innovating in surgical valves. On Sept.29, the company announced a CE Mark for *Inspiris Resilia*, a surgical aortic valve replacement that will be the "first in a new class of resilient" heart valves, according to the company. It is made of the proprietary *Resilia* tissue with many of the same features of the company's established *Perimount Magna Ease* valve with the proprietary *VFit* technology that makes the valve easier to treat with a future valve-in-valve procedure.

Edwards says Resilia tissue is built with proprietary integrity-preservation technology to preserve the tissue and prevent calci-

fication and, unlike many valve replacements, it can be stored dry and ready to use, the company stresses. The CE mark is based on one-year results of the COMMENCE pivotal trial in the US, Canada, and Poland. One-year results from 673 patients in the trial have shown no cases of structural valve deterioration, valve thrombosis or nonstructural valve dysfunction, according to Edwards.

Other notable cardiovascular device approvals in September include the Drug Regulatory Authority of Pakistan's approval of **Shanghai MicroPort Medical**'s *Firehawk* rapamycin-eluting coronary stent, the company's third-generation of drug-eluting stent following the *Firebird* and Firebird2 rapamycin-eluting stents. Firehawk features an "in-groove" abluminal coating and unidirecational-eluting technique that allows it to achieve the same clinical efficacy as stents with much higher drug loads, thereby promoting earlier vascular healing, MicroPort says.

Firehawk has been approved in China since 2014.

APPROVALS IN AUSTRALIA

September was a relatively big month for device approvals from the Australian Therapeutic Goods Administration with three showing up on the Approvals Tracker.

On Sept. 6, Toulouse, France-based **Vexim SAS** announced the TGA-approval of the *SpineJack* implant and *MasterFlow* orthopedic-cement delivery system for surgery to treat vertebral compression fractures. The market for products used in this type of surgery in Australia is worth about €30m annually, according to Vexim.

SpineJack is a small titanium scissor jack. Using specialized instruments created by Vexim, spine surgeons can implant and expand it inside the broken vertebrae with a minimally invasive procedure. MasterFlow, a proprietary system for mixing and accurately injecting orthopedic cement, complements the SpineJack procedure. The procedure restores the spine's optimal shape to eliminate pain and enable the patient to recover their functional capabilities, according to Vexim. SpineJack comes in three different sizes which, the company says, covers 95% of vertebral fractures and all patient morphologies.

Vexim sells SpineJack in Europe through a direct sales force and through distributors internationally. In June 2015, company launched a trial comparing SpineJack to balloon kyphoplasty that will eventually support a 510(k) application for SpineJack to US FDA and says it is looking for the "adequate distribution model for the SpineJack in the US."

Also in September, TGA approved **RTI Surgical Inc.**'s *nanOss Bioactive* bone void filler, an advanced bone graft substitute made of nanostructured hydroxyapatite granules and an open-structured engineered collagen carrier. It's intended for filling bony voids not intrinsic to the bone's structural stability. The company will market it in Australia through **LifeHealth Group Ltd.**

The nanostructured hydroxyapatite provides more surface area to promote cell attachment and is structured to remodel into new bone, according to the Florida-based company. One-year clinical trial data from 46 patients published in 2012 showed that 93% percent of the total individual sites treated with nanOss Bioactive exhibited posterolateral bridging bone.

While announcing the TGA approval of nanOss Bioactive on September 19, RTI Surgical also announced the CE mark approvals for *nanOss Bioactive Loaded* a version of the product sold in a pre-filled mixing syringe, and *nanOSS Bioactive 3D*, nanostructured hydroxyapatite granules suspended in a porous gelatin-based foam matrix. Both will be distributed in Europe through independent distributors, RTI said.

On Sept. 8, TGA approved **Viveve Medical Inc.'s** *Viveve System* for treating vaginal laxity. Vieve uses radiofrequency energy to remodels collagen, which tightens vaginal tissue. The system was approved for commercialization in South Korea in August.

On Oct. 6, US FDA cleared the Viveve System for "general surgical procedures for electrocoagulation and hemostasis." On September 27, the company filed an Investigational Device Exemption (IDE) application to the FDA to launch the VIVEVE II study, a 250-patient randomized sham-controlled trial of the Viveve System. The primary endpoint will be the Female Sexual Function Index (FSFI), according to the Sunnyvale, California company.

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For sortable and searchable tables of all approvals and clearances, check out the Approvals Tracker: https://medtech.pharmamedtechbi.com/datasets/approvals

Boston Scientific Hires Chief Medical Officer

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Prof Ian Meredith will join Boston Scientific as executive vice president and global chief medical officer in January 2017, taking over from Keith Dawkins who will be retiring.

Meredith brings to Boston Scientific more than 25 years of experience as a clinical and interventional cardiologist. He currently serves as professor of medicine and cardiology for Monash University, director of MonashHeart and Monash Health and as executive director of the Monash cardiovascular research center in Melbourne, Australia. His track record as a clinician includes having performed over 10,000 invasive cardiac and coronary procedures and authored more than 200 published papers. Meredith has also been chief or principal investigator on 30 major international multi-center trials, including Boston Scientific's Lotus Valve Reprise research program.

His previous work has focused on the development and clinical evaluation of devices for the treatment of coronary artery and structural heart disease. In his new role, Meredith will be responsible for leading clinical and medical affairs across Boston Scientific, spearheading the company's clinical trial strategy and advancing its pipeline products.

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Inotec Taps Acelity Exec For CEO

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Wound care industry veteran Chad Bateman will join **Inotec AMD** as the new CEO to help promote the company's oxygen based wound treatment product. The privately-held UK company makes specialist mobile medical devices designed to heal chronic and hypoxic wounds.

Bateman has served in several senior executive positions within the wound care industry and joins from wound care and regenerative medicine company, **Acelity LP Inc.** (formerly Kinetic Concepts), where he was vice president and general manager of Europe. He also has twenty years' experience in sales and marketing, working in other established medtech organizations such as **Olympus Corp.** and **CR Bard Inc.**

Bateman will be in charge of leading the commercialization of Inotec's primary product *Natrox*, a mobile medical device that uses oxygen to treat wounds and other health conditions. The company, established in 2005, received venture capital funding in April and had since been building its sales and business team.

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Nanobiotix Expands US Leadership Team

French nanomedicine specialist **Nanobiotix SA** has appointed two new US senior executives, as the company aims to reinforce its presence in the region. Mihail Obrocea has been appointed head of US clinical development and Noël Kurdi director of investor relations.

In the US, Nanobiotix has just submitted its Investigational new drug application (IND) for its prostate cancer treatment, *NBTXR3*, and plans to initiate a Phase I/II trial in three US based oncology sites. The company's products are based on its NanoXray platform, which uses nanoparticles injected or applied to the tumor to increase the effectiveness of radiotherapy and reduce damage to healthy tissues.

Mihail Obrocea joins the company from **SFJ Pharmaceuticals Inc.** where he was vice-president of clinical and medical affairs. Prior to that, he served as project director and oncology clinical lead at **AbbVie Inc.,** leading multiple Phase I and II oncology and hematology clinical trials. He also held the position of vice-president and head of clinical development oncology at **MannKind Corp.** where he brought two cancer vaccines programs into the clinical stages. His experience in the oncology field will be used to advance clinical development of NBTXR3.

Noël Kurdi joins Nanobiotix from the Trout Group & Trout Capital, where she was a senior associate. She previously worked in institutional equity sales and research at Brean Capital, LLC. Nanobiotix already has a subsidiary in Cambridge and has now opened an office in New York to increase its visibility and accessibility to the financial community.

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