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Medtech Insight

Issue 54

medtech.pharmamedtechbi.com

Pharma Intelligence Informa

July 31, 2017

# Medicare Agency Solicits Input On ICD Coverage For First Time Since 2005

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The US Centers for Medicare and Medicaid Services is considering updating its national coverage policy for implantable cardioverter defibrillators for the first time in twelve years.

The agency formally opened the review of its national coverage policy for ICDs – Section 20.4 of the Medicare National Coverage Determinations (NCD) Manual – on May 30 and collected comments through June 29. It expects to release a decision memo by the end of November and complete the national coverage analysis by the end of February 2018.

Unlike most NCD reconsiderations generated by CMS itself, this one does not specify any particular questions the agency is trying to address. But stakeholders who spoke to *Medtech Insight* said that the review is overdue since the current policy is so old and so much clinical evidence on ICDs has been collected since the last review.

In 2003, results of several trials – especially MADIT II and SCD-HeFT– convinced CMS to extend Medicare coverage for ICDs to include the so-called "primary prevention" populations – heart failure patients who have not had a life-threatening arrhythmia before, but who are at risk of sudden cardiac death (SCD) due to electrophysiological complications triggered by their heart failure. The agency first agreed to cover some of this population in 2003. *(Also see "CMS Drops QRS Restriction From Defibrillator Policy, Requires Registry" - Medtech Insight, 4 Oct, 2004.)* The publication of data compelled the agency to expand the covered indications again in 2004 and 2005. *(Also see "CMS Expands ICD Coverage In Long-Awaited Decision; Stakeholders Rejoice" - Medtech Insight, 31 Jan, 2005.)* However, CMS conditioned Medicare coverage of ICDs on participation in the American College of Cardiology's National Cardiovascular Data Registry, thus making the ICD coverage policy one of CMS' very first Coverage with Evidence Development (CED) policies. *(Also see "Coverage-With-Evidence Policy May Force Small Firms To Sell Out – Richner" - Medtech Insight, 23 May, 2005.)*

The ICD policy has not been reopened for reconsideration since then, and many of the 35 comments recently submitted during the initial comment period address the primary prevention or prophylactic indications for ICDs that were the focus of so much controversy and research in the early 2000s. And several stakeholders suggest that the CED evidence-collection

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a young but already profitable US company specializing in regenerative bone technologies, UK regenerative medicine firm Tissue Regenix will significantly bulk up its portfolio and accelerate its global commercial growth plans.



### R&D



### POLICY & REGULATION

# New Interpretation Of Current EU Rules Threatens Procedure Packs

**AMANDA MAXWELL** amanda.maxwell@informa.com

Some notified bodies are starting to aggressively enforce existing rules around procedure packs and systems; they are refusing to certify them unless the company involved has been through a full conformity assessment of all the products involved.

Procedure packs are found in all aspects of the health-care system, gathering together a range of different medical devices – very often as many as 15 or 20, and from different manufacturers – in a single pack targeted towards a specific medical procedure.

Under Article 12 of the Medical Devices Directive, according to *Medtech Insight* sources, there are two types of system and procedure packs, and the regulatory route depends on which category the packs fall:

- In one case, a company puts together various medical devices and instruments in a single box and sells it without making any changes to the labeling or packaging. In this case, the historic understanding is that those who put together these packs may go on sell them without going through the necessary full conformity assessment, as long as they have checked the mutual compatibility of the devices, supplied the relevant information and instructions, and there are internal methods of control and inspection.
- The second case applies to those who resterilize procedure packs. Although the law allows for the resterilization of procedure packs under Article 12, when the sterilization is done in accordance with the original manufacturer's instructions, in practice this is not feasible with devices from 15-20 different manufacturers. In this case, companies must treat the procedures pack or system as a device in itself and go through the full conformity assessment procedure for the pack.

Shutterstock: Sherry Yates Young

## What are procedure packs and systems?

Procedure packs and systems save doctors and nurses time by providing all items in one pack in the order in which they are needed for a specific procedure. Traceability is also streamlined.

An example of a system would be all the parts and accessories needed for a joint replacement surgery. An example of a procedure pack would be a first aid kit or an orthodontic kit.

Because of the positions taken by some authorities and their apparent influence on some notified bodies, the interpretation of the current Medical Devices Directive rules around procedure packs and systems means that those who put them together under the second bullet point, are increasingly being treated as virtual manufacturers for each device in the procedure pack.

This means that instead of having a conformity assessment procedure for the pack as a unit, companies that compile a procedure pack need to go through the full conformity assessment procedures for each device in the pack, even though each of the companies that supply the original devices within the pack will have already done this. Those putting the packs or systems together will also need to supply all the technical documentation for each of the products in the pack, and cannot show the original manufacturer name, nor the CE marking on any of the individual products.

This goes against the historic interpretation of the Directive's rules and could make the practice of putting together procedure packs unmanageable and unprofitable, multiple industry experts, who wish to remain anonymous, told Medtech Insight.

At the moment, there is a high level of concern and uncertainty among manufacturers about this issue. The EU MedTech Europe trade association confirmed to *Medtech insight* that it is planning to create an internal ad-hoc group to work on the Medical Device Regulation requirements for systems and procedure packs. The group emphasizes that this is a matter that industry wants addressed, warning that, otherwise, the advantages offered by systems and procedure packs in surgery and to the health-care system generally, will be lost.

Competent authorities, it seems, are after some clarification to ensure the current regulatory framework under the MDD is being properly interpreted. It seems that one competent authority will ask the Competent Authorities for Medical Devices (CAMD) group to coordinate a market surveillance program on procedure packs and systems in an attempt to persuade the Commission that device-specific guidance is needed.

*Published online 07/18/17*

## What Article 12 of the MDD says on the procedure for systems and procedure packs, and the procedure for sterilization:

- Those who put CE-marked devices together within their intended purpose and within the limits of use specified by their manufacturers to place them on the market as a system or procedure pack, must draw up a declaration stating that they have:
- (a) verified the mutual compatibility of the devices in accordance with the manufacturers' instructions and carried out operations in accordance with these instructions; and
- (b) he has packaged the system or procedure pack and supplied relevant information to users incorporating relevant instructions from the manufacturers; and
- (c) the whole activity is subjected to appropriate methods of internal control and inspection.
- If these conditions are not met, for example the system or procedure pack incorporate devices which do not bear a CE marking or where the chosen combination of devices is not compatible in view of their original intended use, the system or procedure pack shall be treated as a device in its own right and as such be subjected to full conformity assessment procedures.
- Those who sterilize such systems or packs, or other CE-marked medical devices designed by their manufacturers to be sterilized before use, must sterilize them in compliance with the Directive and involve a notified body in aspects of the procedure relating to the obtaining of sterility until the sterile package is opened or damaged. They must draw up a declaration stating that sterilization has been carried out in accordance with the manufacturer's instructions.
- These systems and packs do not need to feature an additional CE marking. They shall be accompanied by the information supplied by the manufacturers of the devices which have been put together.

# You Say Goodbye, I Say Hello – MHRA Moves In, EMA Moves Out

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The UK Medicines and Healthcare products Regulatory Agency is on course to move next year to Canary Wharf, the east London financial district that the European Medicines Agency currently calls home but is being forced to leave as a result of the UK's decision last June to leave the EU.

The MHRA is due to move from its central London location of Victoria to a new government hub in Canary Wharf in the first half of 2018, according to the agency's newly published 2016/17 annual report. It is not known yet when, or to where, the EMA will move.

The move appears to be part of a big government cost-cutting initiative that involves moving thousands of civil servants to a modern government hub in Canary Wharf.

The MHRA comprises three centers – the MHRA regulator, the Clinical Practice Research Datalink and the National Institute for Biological Standards and Control – and, according to its latest annual report, it employed around 1,257 permanent full-time equivalent staff last year.

The report notes the move could lead to the loss of key staff "if they perceive they are moving to a less accessible location with inadequate space and facilities, which would cause disruption to the agency's operations." The MHRA says it is planning to develop "appropriate measures" to

mitigate the impact on staff. Its relocation team will develop an internal communications program to keep staff informed.

An MHRA spokesperson told *Medtech Insight* that "with the move not expected to happen before mid-next year, there is currently no evidence to suggest staff are leaving the agency as result of the planned move." The spokesperson added that the agency was pleased to have secured modern new accommodation and that it was "currently seeking feedback from staff on how they may be impacted by the move for consideration by the move project team."

An "Accommodation Needs and Vision Project" group has produced a report setting out the agreed "vision" for the agency's future accommodation and requirements for the move, according to the annual report. This involves having work environments that will be "inspiring and productive, supported by reliable and effective technology, enabling us to choose flexible work-styles," the MHRA said. "This will enable us to deliver the Agency's mission, encourage a more inclusive, collaborative and professional culture, and provide the best service to our stakeholders and customers."

## UGLY, FRAGMENTED OFFICES

The government first announced it would be moving 5,700 full time civil and public servants from their offices in central London to east of the city in December last year. The move, which is due for completion by the end of 2018, is part of a drive to modernize the civil service. "Relocating civil and public servants from existing, often fragmented office locations, to modern, cross-departmental workplaces will make the most of emerging working practices and technology is part of that drive," the government said. The new hub in Canary Wharf would provide "a better working environment for many London-based Civil Servants at considerably less cost to the taxpayer." The approach will be replicated across the UK, "putting right the historic mistake of forcing public servants to work in ugly and expensive buildings."

## GERMANY WANTS BONN TO HAVE EMA

EU member states wanting to house the EMA post-Brexit – the UK is due to leave the EU at the end of March 2019 – must submit their bids by the end of July. A decision on the new location of the agency is expected in November. *(Also see "EU Postpones Decision On EMA's New Home To November" - Medtech Insight, 23 Jun, 2017.)* Perhaps then there will also be some clarity around the timing of its departure from London.

Germany is joining the ranks of those bidding to host the EMA, which currently employs almost 900 people. Germany would house the agency in Bonn. Many countries are competing for the agency in addition to Germany, including Sweden, Denmark, Ireland, France and Spain. The official website for the Bonn candidacy is www.closer-to-europe.eu.

The EMA is involved in assessing combinations of medical devices with ancillary medicinal products that are derived from human blood, for example surgical sealants containing albumin, as well as in certain medicines, where the EU's centralized procedure is necessary.

*Published online 07/20/17*

# Brexit Health Alliance Adds To UK-EU Debate; Medtechs Settle Into Interim Brexit Pace

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UK "Brexit secretary" David Davis met his EU counterparts for the second round of withdrawal talks this week in Brussels. No one expected great progress from the sessions, but few could have expected so little. It's an indication that the UK government is increasingly unhappy in its own skin and is newly beset by Brexit uncertainties of the kind that it inflicted on the country at large with such apparent alacrity just a year ago.

If a UK election were held today, 45% of the electorate would vote for the current opposition, leaving the ruling Conservatives trailing at 40%, according to the July 10-11 YouGov poll. UK BioIndustry Association (BIA) Chief Executive Steve Bates told his monthly Brexit webinar audience (July 19) that the government's implausible post-election weakness has meant that many positions on EU withdrawal – on "hard" Brexit especially – have moved a lot in the past month. Brexit, it seems, is not a "done deal" and the government is engaging with industry in a new way, as PB Consulting's Paul Bristow observed during the Association of British Healthcare Industries' recent Brexit Question Time (June 28). *(Also see "UK Medtech One Year Post-Brexit Vote: Still In The Land Of Uncertainty" - Medtech Insight, 30 Jun, 2017.)*

Bates also mentioned that applications to host the European Medicines Agency, currently headquartered in London, must be in by July 31, and a decision will be made during or after the EU General Affairs Council meeting of November 14-15. The BIA was evidently gratified by the flurry of open letters published in the *Financial Times* in recent weeks showing that the UK health ministry and life sciences industries want to retain a close relationship with the EU in matters of regulation.

The inaugural meeting of the NHS Confederation's Brexit Health Alliance, held yesterday (July 19), was largely an organizational affair that will be followed up at three-monthly intervals. Detail from the meeting will emerge next week. The Alliance, announced in mid-June, aims to bring together 14 stakeholders, including the NHS, medical research, industry, patients and public health organizations. It is overseen by co-chairs Sir Hugh Taylor, former permanent secretary Department of Health, and Niall Dixon, chief executive of the NHS Confederation.

### UK MUST BE ALIVE TO MDR/IVDR ADOPTION SCENARIOS

Testifying to the volume of activity in June and July, Alison Dennis, a partner with law firm FieldFisher, wrote in the ABHI's Brexit blog (July 19) that the publication of the so-called "Great Repeal Bill" on July 13 will, when enacted into UK law, deftly sweep EU laws onto the UK statute book as UK laws – but it won't be all plain sailing.

A potential problem arises with the EU Medical Device and IVD Regulations, which will become directly effective in EU member states as of the dates that the different provisions come into force, Dennis writes. Most of the provisions will be enacted *after* the UK's scheduled departure date (March 29, 2019 – unless extended). Thus, the UK will have to proactively take steps to separately enact the provisions of the two regulations into UK law. If it doesn't, the by-then outdated trio of EU Directives (Medical Devices Directive, Active Implantable Medical Devices Directive and IVD Directive), converted into UK law, will have primacy in the UK.

Concerned at this potentially disastrous course of events, Dennis has taken time to explain the situation to UK junior health minister Lord O'Shaughnessy (who recently delighted industry with Accelerated Access Review – AAR – funding pledges *(Also see "UK Device, IVD Sector Cheered By New Funding Pledge For Accelerated Access Program" - Medtech Insight, 14 Jul, 2017)*. She said she impressed upon him the need to be alert to the risk of this major backwards step for UK medical device regulation.

### ABHI FOLLOW-UP SURVEY OF BREXIT ATTITUDES

Regulation in the post-EU era is the major Brexit preoccupation for UK based-medtechs, but as delegates learned at the ABHI Question Time panel (which featured legal expert Dennis), there are mixed views on the current significance and impact of Brexit on UK medtech trade after March 2019. ABHI market access director Andrew Davies provided more detail on the June 2017 Brexit survey findings that were reported at last month's ABHI Question Time at a June 29 Westminster Health Forum (WHF) meeting.

Brexit is currently viewed as a top challenge by 53% of UK companies polled (unchanged since 2016), but access to the NHS has become their overriding concern (70%, up from 46% in 2016). A reduced 37% (down from 52% in 2016) say investment decisions are being put on hold, and only one fifth (down from one third) say that commercial opportunities are being delayed. And 60% (up from 30%) have seen increases in manufacturing costs since the June 2016 referendum. On the question of whether companies are seeing increased opportunities to trade outside the EU, 42% (compared to 37% in 2016) say it is still too soon to tell.

Davies told the WHF meeting that the survey shows that there is no clear picture yet on trade post-Brexit, but that there is a lot of cost pressure in the system.

The initial shock of Brexit has been absorbed by UK medtechs, and although the ABHI survey produced a mixed bag of findings, there is a pervading sense of damage limitation, rather than anything approaching confidence. In this busy summer of Brexit positioning, industry awaits the next chapters with nervous anticipation.

*Published online 07/20/17*

# Alere Off-Loads Blood Gas Business To Siemens

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**Siemens Healthineers** will acquire **Alere Inc.**'s **Epocal Inc.** blood-gas analysis business for an undisclosed sum when **Abbott Laboratories Inc.** completes its planned acquisition of Alere, Siemens announced July 21.

Epocal, which Alere acquired in 2013 for about $166m, develops and markets point-of-care blood diagnostic systems for healthcare providers, most notably the handheld wireless *epoc* blood analysis system. Financial details of the transaction are not being disclosed. The companies said the deal is subject to the completion of Abbott's acquisition of Alere, as well as antitrust approvals and other customary closing conditions.

This is Alere's second sell-off in the past week to meet US and EU antitrust requirements for the pending $5.4bn deal with Abbott. On July 18, Alere announced plans to sell its BNP reagent and Triage business to Quidel Corp. for $440m, pending the completion of the Abbott deal. *(Also see "Alere Unloads Its Triage Assets To Quidel" - Medtech Insight, 19 Jul, 2017.)* In January, the European Commission cleared the deal on the condition that Alere sell the Epocal, BNP, and Triage businesses. *(Also see "EU Approves Troubled Abbott-Alere Deal – But Abbott Still Wants Out" - Medtech Insight, 26 Jan, 2017.)*

Epocal's epoc is a handheld, wireless device that measures blood gas, electrolyte, and metabolite results at the point of care in about 30 minutes. It includes the epoc single-use BGEM test card, a reader, and *host2* mobile computer. The BGEM test card features smartcard technology with a full menu of tests.

Siemens currently markets the *RAPIDLab 1200* high-volume blood gas system for critical care sites, the *RAPIDPoint 500* analyzer for fast point-of-care testing, and *Multicap* capillaries for blood sampling. The systems are integrated with the *RAPIDComm* data management system.

"The acquisition of the epoc product line will enable us to provide the right solution in the right setting, all from one partner," Peter Koerte, president of Siemens Healthineers point of care diagnostics, said in a release. "The epoc product line will seamlessly integrate with our digital ecosystem offering customers the broadest solution available in the market. The acquisition complements our existing offerings in the point of care diagnostics space, with a view to provide customers globally with a full range of blood gas solutions."

*Published online 07/24/17*

# Insulet, Ypsomed Split Up And Go Head-To-Head In Insulin Pump Market

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Massachusetts-based maker of the Omnipod insulin patch pump**Insulet Corp.** has announced it will split from its European distributor Ypsomed from June 30, 2018 and take complete ownership of its insulin patch pump – the Omnipod Insulin Management System.

Ypsomed has held exclusive rights to distribute the Omnipod in Europe and other markets outside the US since 2010. During this period, the company has managed to garner a market share of up to 20%. Ypsomed stated that the reason for not continuing the partnership was that the companies had failed to agree on extending the contract as the price demanded by Insulet, "would have made continued economic viability impossible." The Swiss company currently has an insulin patch pump, YpsoPod, in its portfolio, which is marketed under the company's mylife Diabetescare brand. It announced it will introduce mylife YpsoPod in the mid-term and "overcompensate the shortfall of the Omnipod business after a transition phase."

"The separation from Insulet Corp. is unfortunate as we will be losing a large proportion of sales and profit in our Ypsomed Diabetes Care segment during the business year 2018/19. Based on last year's final figures, this amounts to CHF120m ($97.6m) in sales and CHF24m in operating profit," said Ypsomed CEO, Simon Michel. However, looking on the positive side, Michel added: "We will be compensated for our successful work with approximately $50m, two year's profit and the profit won't be diluted through this trade product in the future. Furthermore, this gives us a number of opportunities: we will be able to respond much more flexibly on the market with our current and future portfolio and are not dependent on a contractual partner. Distribution agreements severely restrict freedom of action."

Insulet said it will assume the distribution, sales, marketing, training and support activities of the system across Europe from July 1, 2018.

Insulet ranks third in the insulin pump global market with an estimated $277.1m in sales in 2015 accounting for a 7.5% market share, according to figures from *Meddevicetracker*'s Global Diabetes Management Devices Market report. Omnipod is a wearable, disposable, waterproof self-adhesive patch pump primarily used for the treatment of type 1 diabetes. The system provides up to 72 hours of continuous insulin delivery and is a smaller competitor to the systems sold by **Medtronic** and **Animas/Johnson & Johnson**. *(Also see "Advent Of Artificial Pancreas Tech To Galvanize Fast-Growing Diabetes Market" - Medtech Insight, 26 Apr, 2017.)*

Insulet has direct commercial operations in the US and Canada but said assuming distribution would strengthen its financial position and expand its European presence. The company will be hoping to capitalize on the growing diabetes market which, according to a report by Meddevicetracker, is forecast to grow from $9bn in 2015 to $11.2bn by 2020, a CAGR of 4.5%.

*Published online 07/21/17*

# Class I Recall On Penumbra Revascularization Device

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Wire in Penumbra Inc.'s *3D Revascularization Device* can endanger patients by breaking or separating during use, US FDA said in announcing a voluntary class I recall of the device.

Class I recalls are reserved for issues that could lead to serious injuries or death. In this case, the recall follows reports of a delivery wire within the revascularization device breaking or separating during use. "Fractured pieces of the delivery wire could be left inside the patient's brain bloodstream, and this or the attempts made to retrieve the fractured pieces, can make the stroke worse," FDA said in the recall notice, adding that wire breakage could also lead to continued blockage of blood vessels, completion of the stroke, and death.

The Penumbra 3D Revascularization device is a component of the *Penumbra System*, which works to restore blood flow or remove blood clots from blood vessels in the brain during a stroke. It is approved for use in patients who are ineligible for or fail intravenous tissue plasminogen activator (IV t-PA) therapy.

The recall affects four lots of the revascularization devices made between March 31, and April 28, 2017, and distributed between May 15 and June 7, 2017. A total of 155 units were sold in the US, the FDA recall notice states. Penumbra contacted its customer about the issue on June 9, and is asking clients to quarantine affected devices and contact the company for replacements.

Penumbra, which staged an initial public offering in 2015, raised $92.9m during a funding round this March. *(Also see "Deals Shaping The Medical Industry, April 2017" - Medtech Insight, 5 Apr, 2017.)* The company's stock hit a 52-week high of $91 on June 26 before dipping slightly. Shares were valued at $84.40 as of July 24.

*Published online 07/24/17*

# 'Profitable, High-Growth' CellRight Bulks Up Tissue Regenix's Ortho Biz

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**Tissue Regenix Group PLC** (TRX) is acquiring **CellRight Technologies**, a US bone regeneration technology specialist, in a deal worth up to $30m. The acquisition is the first for Leeds, UK-based TRX and will significantly flesh out the company's portfolio – which has only one product being sold on the market – with 13 other products that are already being commercialized in North America and beyond.

TRX currently sells in the EU and US its *DermaPure* wound care product, which brought in revenue of £1.4m in 2016. The tissue scaffold is based on the firm's proprietary *dCell* decellularization technology which removes DNA and other cellular material from animal and human tissue to prevent rejection by the patient's body when it is implanted. The company also has a cardiovascular product, *CardioPure*, and an orthopaedic product, *OrthoPure*, but neither are approved yet.

CellRight's substantially larger portfolio, as well as a pipeline of products in development, will enable TRX to better target the lucrative orthopaedic regenerative medicine market, which represent a $1.7bn opportunity in North America alone.

CellRight has developed different forms of bone grafts, based on its osteoinductive demineralized bone matrix (DBM) platform, for a range of orthopedic surgical applications including spine, trauma, foot & ankle and sports medicine. It launched 13 products into the market over the last three years and the compound annual growth rate from sales during this period has been in excess of 61%. In 2016, the firm recorded revenue of $5.6m and earnings of $1.5m. Its performance this year so far also looks promising, with unaudited figures showing revenue for the first five months to be around $2.6m, representing a 21% year-over-year growth.

Driving CellRight's sales growth are the MatrixCellect line of demineralized bone matrix putty and bone graft constructs, said TRX CEO Antony Odell, adding that another measure of CellRight's success is in the number of significant customer relationships it has established in a short time. It has private-label customers and also sells products through a well-established distribution network. "They have a number of very important clients in their books. They have shown that they have developed some of the most innovative technologies in this space and it is very encouraging that the big players are looking very seriously at these products," Odell told *Medtech Insight*. TRX estimates the acquisition would immediately increase its US sales by 2.5 times and speed up the company's path to profitability, which it is targeting for 2020.

While the bulk of CellRight's sales are in North America, the firm also has some presence in the Middle East, South Korea, and South America, and TRX would be looking to leverage these international sales channels.

As part of the acquisition, TRX will also gain CellRight's FDA- and AATB-accredited tissue processing facility in San Antonio, Texas.

Odell said TRX had first started talking to CellRight back in 2013 when it was looking for a contract manufacturer and tissue bank in the US for DermaPure. The timing, however, wasn't quite right then, with CellRight having only just been established as a company a year before and TRX ended up partnering with Community Tissue Services, "a much larger entity," instead. "CellRight at that time was at an early stage of growth and it was focused on building its own business, rather than on these types of deals; they didn't want to process tissue," said Odell. But since then, CellRight has evolved from being the "vanilla" tissue bank and potential subcontractor that TRX had viewed it to be to in 2013, to an emerging, revenue-generating player in the bone graft market. "They've done some very interesting things with their proprietary bone technology, and developed into a profitable business in a very short space of time."

The $30m acquisition price includes an upfront payment of $25.9m plus an additional $4.1m in revenue performance-related milestones. To help fund the acquisition, TRX will be looking to raise £40m through a share offering. The firm is issuing up to 400 million new shares at a price of 10p per share.

On closing the CellRight deal, the current CEO of the firm, Jesus Hernandez, will continue to run the San Antonio, Texas operation and take on the title of chief scientific officer at TRX.

*Published online 07/20/17*

# Agendia Touts ASCO Guideline's Endorsement Of MammaPrint Breast Cancer Test

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**Agendia BV** hopes adoption and reimbursement for its *MammaPrint* 70-gene breast cancer risk-of-recurrence test will get a boost from new American Society of Clinical Oncology guidelines (ASCO) that specifically recommend MammaPrint.

A focused update to ASCO's practice guidelines on biomarkers to guide decisions on adjuvant systemic therapy for women with early stage invasive breast cancer, published in the *Journal of Clinical Oncology* American Society, specifically highlight MammaPrint as the only genomic test that can inform treatment decisions for women with estrogen receptor-positive or progesterone receptor-positive, HER2-negative breast cancer with lymph node negative, or one to three positive lymph nodes who are at a high clinical risk of recurrence.

The ASCO announcement comes soon after the 5th St. Gallen International Breast Cancer Guidelines, published in the *Annals of Oncology* on July 6, recommended the MammaPrint to help guide treatment decision-making for patients with early-stage breast cancer. The St. Gallen guidelines had recommended MammaPrint before, but the 2017 update expands the panel's consensus on MammaPrint to include use as a prognostic tool for treatment decisions for post-surgery chemotherapy in patients with lymph-node positive breast cancer.

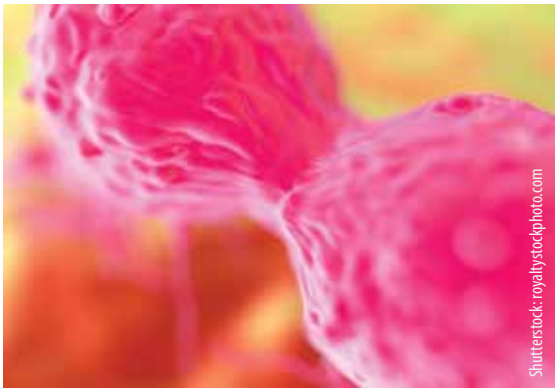
"The ASCO guidelines validate and open up access to patients and thereby patient access for Agendia," Agendia CEO Mark Straley told *Medtech Insight*. "Also, many of the payers in the US and outside the US look at the guidelines to make determinations of reimbursement and payment. … So, having ASCO come out in full-throated support of the MammaPrint [assay] will pay-off – in fact its already begun to pay-off – with payers in the US and outside the US, and will continue to do so." Straley said there are about 31,000 women who are lymph-node positive in the US and about 39,000 such patients in Western Europe. "And our test now is the only one that would be applicable in their diagnosis treatment regimen."

Once the ASCO and St. Gallen guidelines were announced, "We automatically updated our dossiers to all the major payers – the BlueCross/BlueShields of the world, etc.," the CEO said. "Many of them in the US had said, 'When you get major guideline inclusion in the US, submit it to us and it will be a positive move for you.' So, we are in the middle of doing that right now. We're looking for favorable movement. Some will take the rest of this year to complete their payer instructions, but we have already begun seeing payers lock-in payment [for MammaPrint] and we fully expect to see that through the balance of this year."

## MINDACT DRIVES GUIDELINES UPDATE

The authors of the focused update, led by Ian Krop, Dana-Farber Cancer Institute in Boston, explain that the update was triggered by the publication the MINDACT (Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy) study about a year ago. *(Also see "MINDACT Trial: Agendia's MammoPrint Test Identifies No-Chemo Candidates" - Medtech Insight, 31 Aug, 2016.)* The authors reviewed the MINDACT results along with other published literature on the MammaPrint assay to assess the evidence of clinical utility. MINDACT was sponsored by the European Organization for Research and Treatment of Cancer, Agendia, Breast International Group, Roche Pharma AG, Novartis AG, and Sanofi, and led by Fatima Cardoso of the Champalimaud Clinical Center–Champalimaud Foundation in Lisbon, Portugal.

In the 6,693-patient MINDACT trial, patients with node-negative, ER/PgR–positive, HER2-negative breast cancer Individuals were assessed with the MammaPrint 70-gene signature and clinical factors to estimate their risk of cancer-recurrence. Subjects with both a low clinical and low genomic risk did not receive chemotherapy, and those at high clinical and high genomic risk received chemotherapy. The subjects with discordant clinical and genomic risk results were randomly assigned to chemotherapy or to no chemotherapy.



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The MammaPrint assay could identify patients at a high risk based on clinical factors but a low risk based on their genomic factors who had a favorable outcome when treated with endocrine therapy alone, without chemotherapy. The five-year distant metastasis-free survival rate in this group was 93.9%, which is similar to the distant metastasis-free survival of the women randomly assigned to receive chemotherapy, 95.5%."

"MammaPrint can provide guidance about the prognosis of women with ER/PgR–positive, HER2-negative breast cancer and a high clinical risk but low genomic risk, whose outcome is likely to be favorable even in the absence of chemotherapy," the ASCO guidelines explain.

The guidelines caution, however, that patients with high clinical risk and low genomic risk may get a small benefit from chemotherapy because the MINDACT study was not designed to detect a significant difference in favor of chemotherapy and is underpowered to do so retrospec-

tively. Also, MINDACT included an optional random assignment to anthracycline-containing versus nonanthracycline-containing chemotherapy regimens. Whether the specific chemotherapy assignment affected patient outcome is not yet known. Further, additional follow-up beyond five years as well as investigation of key prognostic subgroups is not yet complete, the ASCO authors point out.

"We were extremely pleased to see the level of recommendations, certainly for the clinically high-risk patients," Straley said. "That is the 'sweet spot' for clinicians and patients trying to decide, should they go for chemo, or can they safely forgo it. If that were all it was by itself, we would have been extremely pleased with that. But the second component [of the guidelines] is that [it designates] MammaPrint as now the only test that is indicated in lymph-node-positive breast cancer patients. Traditionally, treatment for lymph-node-positive breast cancer was always high-risk and 99% of the time, they went on for chemotherapy."

*Published online 07/24/17*



## US APPROVALS ANALYSIS:

# FDA Delivers Strong Half-Year Volumes

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US FDA device approval and clearance numbers came in strong in June, capping off an active half year.

The agency approved seven original PMAs, for completely new, high-risk devices, last month – the highest monthly total for the year. That brings the original-PMA total for the first half of 2017 to 24, five ahead of the first half of 2016 and exactly even with the same-period total in 2015, which was a record year for original PMAs. *(Also see "FDA Hits User-Fee-Era Record For 'Novel' Devices: A New Normal?" - Medtech Insight, 14 Jan, 2016.)*

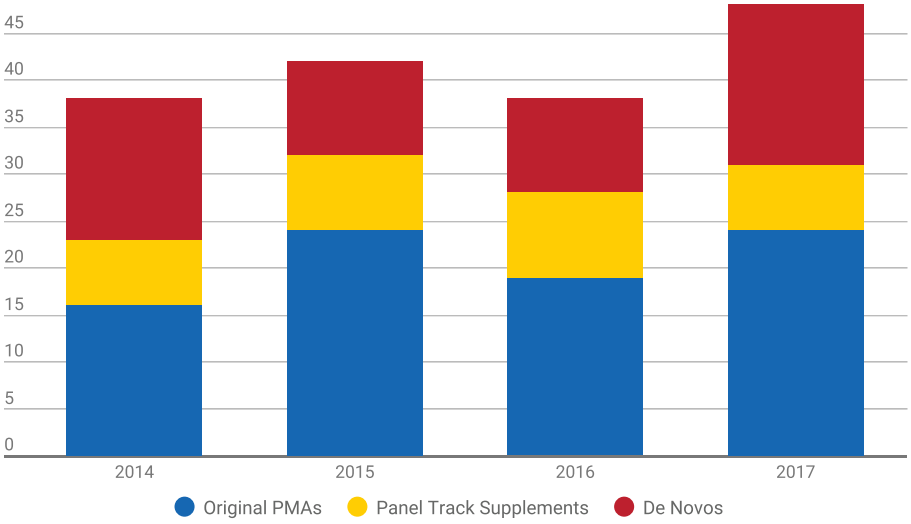
Panel-track PMA supplements, for clinical data-worthy new indications or design changes, are also robust so far this year, with seven approvals through June. That's just two behind last year, when there were a record number of panel-track supplement approvals.

Meanwhile, *de novo* classifications, for low-to-moderate-risk, novel devices, showed the biggest percentage increase in approvals so far this year. FDA granted 17 *de novos* through June, compared to 10 in the first six months of 2016, and another 10 during the same period in 2015. The *de novo* pathway has been more popular since 2013, when Congress made this approval pathway more direct. *(Also see "US Approvals Analysis: Strong Month For IVD De Novos In February" - Medtech Insight, 7 Mar, 2017.)* And user fees and FDA performance review goals linked to them are now established for *de novos* for the

FIGURE 1

### NOVEL DEVICE APPROVALS: Half-Year Totals

Total original PMA, panel-track PMA supplement and de novo approvals recorded January-June, 2014-2017




*Medtech Insight's Approvals Tracker*

FIGURE 2

### Firms With Most 510(k)s, January-June 2017

Totals include divisions and subsidiaries

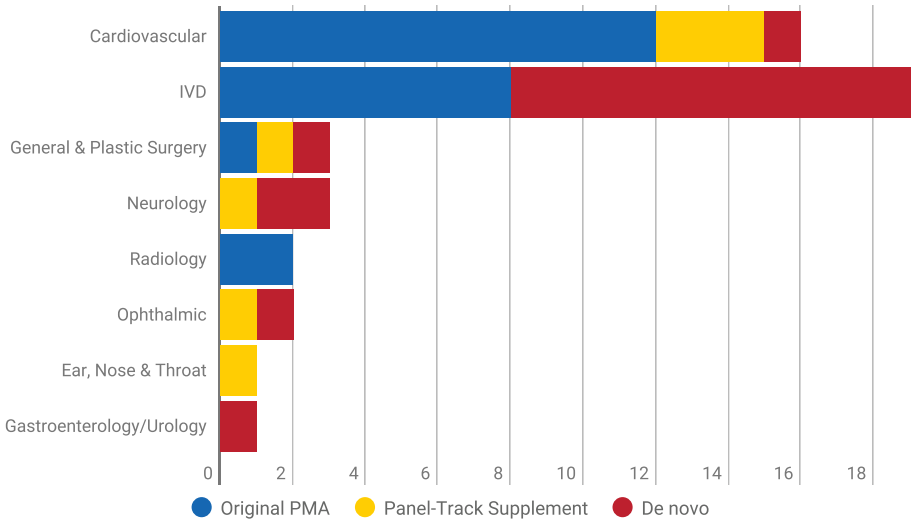

*Medtech Insight's Approvals Tracker*

## Companies With Multiple Novel-Device Approvals

- **Roche/Ventana**: *cobas CMV* molecular diagnostic for cytomegalovirus (June 1/Original PMA); *Ventana PD-L1 (SP263) Assay* (May 1/ Original PMA); *CINtec Histology* test (March 4)
- **Abbott Laboratories/St**. Jude Medical**:** ABBOTT REALTIME CMV *assay* (May 18; Original); MRI-conditional pacemakers and leads (*Assurity MRI*, *Endurity MRI*, *Tendril MRI Lead*, *MRI Activator Merlin PCS* programmer software) (Jan. 31/ Original)
- **Biotronik**: *Astron Pulsar/Pulsar-18* stent system (March 23/Original); *Pro-Kinetic Energy* cobalt chromium coronary stent (Feb. 14/Original)
- **Medtronic**: *Resolute Onyx drug-eluting coronary stent*(April 28/Original); *Melody, Ensemble, Ensemble II*transcatheter pulmonary valve system (Feb. 24/ Panel-Track Supplement)
- **Edwards Lifesciences**: *Edwards Pericardial Aortic Bioprosthesis*(June 29/Original); *Sapien 3* transcatheter aortic heart valve system (June 5/Panel-Track)
- **CR Bard**: *Lifestream*balloon expandable vascular covered stent (April 24/ Original); *Lutonix 035* drug-coated balloon catheter (Feb. 7/Panel-Track)

FIGURE 3

## Novel Device Approvals, By Product Type, January-June 2017




*Medtech Insight Approvals Tracker*

first time under the next device user-fee program, in anticipation of more of these submissions. *(Also see "User-Fee Facts: 10 Key Medtech Details From US FDA Agreements" - Medtech Insight, 11 May, 2017.)*

### 510(K) RACE: MEDTRONIC, SIEMENS ARE NECK AND NECK

The volume of 510(k)s – the regulatory path for most new devices and device updates in the US market – also grew in the first half of 2017. FDA cleared 1,580 510(k)s in the first six months of the year, up from 1,460 in 2016, and relatively even with 2014 and 2015 clearance totals.

510(k) clearances are the basis for the medtech sector's iterative development cycle. And one measure of a company's regulatory and R&D productivity is the number of 510(k)s clearances that it gets through FDA.

As has been the case in recent years, **Medtronic PLC** and **Siemens AG**, including subsidiaries, are battling for the top stop in the 510(k)-clearance count. Both firms track in at 33 clearances during the first six months of 2017, according to *Medtech Insight*'s Approvals Tracker.

**Cook Group Inc.** is next behind in the third spot, and ahead of pace, with 26 clearances through June. That is not far off from the 33 clearances attained by the company throughout all of 2016.

Meanwhile, **Zimmer Biomet Holdings Inc.** is one firm that appears on a slower than normal pace, with only seven clearances so far in the first six months, down from 15 during the same period last year.

One company to watch is **Becton Dickinson & Co.**, which is currently in the middle of completing its $24bn acquisition of **CR Bard Inc**. If the acquisition were complete, the combined company's 510(k) clearance total would be 21, enough to put BD/Bard to fourth on the total's list. (*See Figure 2.*)

For novel device approvals in the first half of 2017, Roche (including its Ventana diagnostics subsidiary) is in the lead with three such approvals, including two original PMA and one *de novo* approval, all *in vitro* diagnostics. Five other firms achieved two novel-device approvals through June.

### MOST NOVEL APPROVALS: IVDS AND CARDIOVASCULAR

Slicing the data by product category, cardiovascular devices and *in vitro* diagnostics accounted for the most approvals so far this year, aligning with previous year trends. (*See Figure 3.*)

Through June, 15 original PMA and panel-track supplement approvals, along with one *de novo*, were reported for cardiovascular devices. While its generally recognized that transcatheter heart-valve devices have eclipsed stents as the hottest area of cardiovascular device development, that was not apparent from the January-June approvals. Seven of the 16 approvals in this space were stent devices, while only three approvals related to transcatheter valves.

Among the seven stent approvals were Medtronic's *Resolution Onyx drug-eluting*

*coronary stent*, the *Tryton Side-Branch Stent* from **Tryton Medical Inc.** and the *Lifestream peripheral artery stent* from CR Bard.

The only transcatheter aortic heart valve (TAVR) approvals on the list is a June 5 panel-track supplement approval for **Edwards Lifesciences Corp.**'s *Sapien* system for "valve-in-valve" procedures and the June 1 de novo classification for **Claret Medical Inc.**'s *Sentinel* cerebral protection systems for TAVR procedures. The other transcatheter valve approval was a supplement for Medtronic's *Melody* pulmonary valve system.

Other cardiovascular device approvals include several others in the valve space, automated external defibrillators, MRI-conditional pacemakers and a ventricular assist device.

For IVDs, there were eight original PMA and panel-track supplement approvals and 11 *de novo* go-aheads. Molecular tests for infectious diseases and oncology drug companion diagnostics made up most of the IVD approvals this year so far.

Roche gained original PMA approval for its *cobas cytomegalovirus assay*; **Thermo Fisher Scientific Inc.**achieved approval for its *Oncomine Dx Target Test*first-of-a-kind multi-drug next-generation sequencing companion diagnostic; and **Illumina Inc.**earned approval for its *Praxis Extended RAS Panel* as an aid to treatment for patients with colorectal cancer.

Cardiovascular devices and IVDs far outpaced any other category. The next most frequent approvals were for general and plastic surgery and neurology devices, which netted three each.

*Published online 07/20/17*

**CLICK**
For sortable and searchable tables of all approvals and clearances, check out our Approvals Tracker at http://bit.ly/29QApYR

## OUS APPROVALS:

# Neurostim And Cardiovascular Lead June Surge

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More medtech approvals from outside the US were announced in the first half of 2017 compared to the first eight months of 2016, putting this year on pace for almost 50% upsurge.

In June, 36 new approvals from countries other than the US appeared on *Medtech Insight*'s Approvals Tracker, bringing the total for 2017 to 182. 2016's list of non-US approvals did not reach 182 until mid-September. If the second half matches the first half, 2017 will finish with 364 non-US approvals, compared to 241 in 2016.

June brought a relatively big haul of approval announcements, with 36, a big increase over the ten in May. The total for June was also an increase over June 2016, which had 31 approvals outside the US. *(Also see "OUS Approvals Analysis: IVDs Lead A Slow Month" - Medtech Insight, 14 Jun, 2017.)*

### BIG MONTH FOR NEUROSTIM APPROVALS

In most months, *in vitro* diagnostics are the most common type of device appearing on the approvals list, followed by orthopedics and/or cardiology, and a few each in other categories. But in June, there were 14 approvals for neurostimulation systems, nine for cardiovascular devices, and three orthopedic approvals. There were two IVD approvals and no more than two in any other category.

The list of neurostim approvals last month was led by **electroCore LLC**'s *gammaCore* vagus nerve stimulation system. The product is already CE marked for treating migraine and severe headaches but the latest includes more indications. According to *Meddevicetracker*, as of June 22, gammaCore has a CE mark for treatment of seizure disorders, major depressive disorder, irritable bowel syndrome, generalized anxiety disorder, as well as migraines and other headaches. However, electroCore has not provided details on the dates that gammaCore has gained CE marked for these additional indications.

The company also disclosed gammaCore has been granted regulatory approval for the acute and/or prophylactic treatment of cluster headache, migraine and medication-overuse headache in New Zealand and Australia. This further expands the geographic reach of gammaCore for headaches; the device is already approved for acute and/or prophylactic treatment of cluster headache, migraine and medication-overuse headache in South Africa, India, Colombia, Brazil and Malaysia. In Canada, gammaCore is approved for cluster headache and treatment of migraine.

The company announced June 15 that the US FDA granted 510(k) clearance to market a newer version of gammaCore, called the *gammaCore-S* – for the acute treatment of pain associated with episodic cluster headache. The original version earned a *de novo* approval in April. *(Also see "US Approvals Analysis: April A Big Month For Non-Invasive Neurostim" - Medtech Insight, 5 May, 2017.)*

A few other neurostimulation devices earned approvals outside the US in June. On June 6, **Boston Scientific Corp.** announced that it received a CE mark for the *Vercise Gevia* MRI-compatible deep brain stimulation (DBS) system for the treatment of movement disorder symptoms in patients with Parkinson's disease and a CE mark for Vercise Gevia to treat dystonia and essential tremor. Vercise Gevia features the *Vercise Neural Navigator 2* and unique *STIMVIEW* programming software, which lets clinicians visualize the stimulation field while configuring a DBS stimulation program.

The approval expands the Boston Scientific's *Vercise Directional* portfolio, which are the only DBS systems that can finely control the size, shape and direction of stimulation with multiple independent current control technology, according to

# OUS Approvals

June's non-US approvals was dominated by the 14 neurostimulation approvals, including five new CE Marked indications for electroCore's gammaCore system.

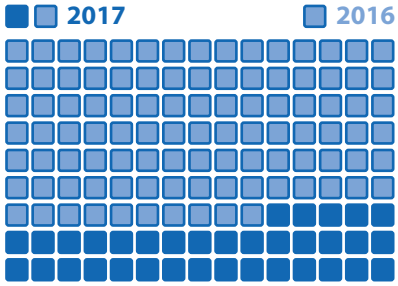
**36 APPROVALS**
28 CE Marks

The 36 non-US approvals represents **a big jump** from the 10 in May and is five more than the number of non-US approvals in June 2016.

**2017 reached 182 non-US approvals by mid-year.** 2016 didn't reach 182 until September.

**182**
**NON-US APPROVALS**

JUN 2017
SEP 2016

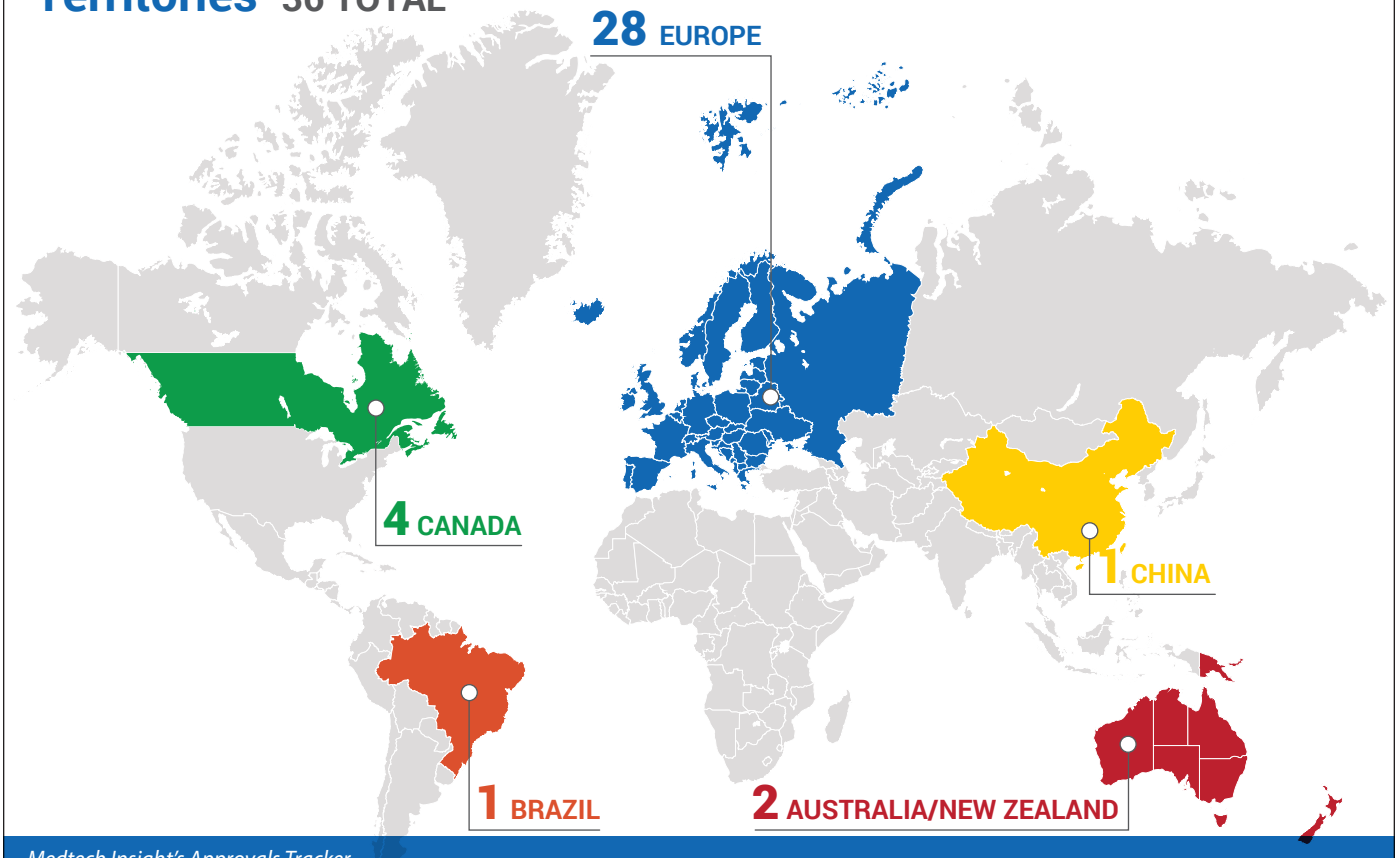



**2017 is on pace for 364 non-US approvals,** compared to 241 in 2016.

## Product Categories
36 TOTAL

- **14** Neurology/Neurostim
- **9** Cardiology
- **3** Orthopedics
- **2** Diabetes
- **2** In Vitro Diagnostics
- **2** Monitoring
- **2** OB/GYN
- **1** Oncology
- **1** Wound Therapy

## Territories 36 TOTAL




*Medtech Insight's Approvals Tracker*

Boston Scientific. In May, the company said it expects to launch the Vercise DBS in the US by the end of the year. *(Also see "Pain Management II: Competition Intensifies For Spinal Cord Stim Market's Big Three" - Medtech Insight, 23 May, 2017.)*

Also on June 6, **Medtronic PLC** announced that Health Canada has licensed its *SureTune 3* software for deep brain stimulation. According to Medtronic, SureTune 3 allows for more precise, efficient DBS treatment and improves patient management with centralized data storage for easy reference. The software provides patient-specific visualization of lead location and shows a simulated volume of neural activation to help physicians plan DBS therapy. SureTune 3 is an upgrade over SureTune 2, which earned a CE mark almost a year ago. *(Also see "OUS Approvals Analysis: Expanded CoreValve Indication And Zika IVDs Among August's CE Marks" - Medtech Insight, 14 Sep, 2016.)*

Among the cardiovascular approvals, **Lifetech Scientific (Shenzhen) Co. Ltd.**'s announcement that its *LAmbre* left-atrial appendage closure (LAAC) system is now approved in China accompanied news that the company is set to start a US trial of LAmbre and that it has launched a 500-patient, three-year global post-market study of LAmbre in Europe, Asia, and South American. LAmbre earned a CE mark in June 2016.

Lifetech is one of several firms chasing LAAC market leader Boston Scientific, whose *Watchman* LAAC gained a big head start on the US market with its 2015 FDA approval. The device is increasingly accepted by implanting physicians, patients, and payers, which should ease the path to the US market for any LAAC devices that try to compete with Watchman. *(Also see "Earnings Winners and Losers: BSX, EW, ABT, JNJ, SYK, ZBH" - Medtech Insight, 8 Feb, 2017.)*

*Published online 07/19/17*

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# numares Targets 2018 For Metabolomic Bladder Cancer Test

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**numares is targeting 2018 for a launch of a bladder cancer test based on its metabolomic biomarker network technology**

German IVD diagnostics firm **numares** is targeting 2018 for the European launch of a bladder cancer test based on its metabolomic network technology. numares obtained promising results from a retrospective study showing evaluation of metabolomic biomarker networks from urine samples can be used as a diagnostic for bladder cancer. Based on the results, the company has enrolled patients in a prospective study for validation.

Founded in 2004 as a spin out from the Institute of Biophysics at the University of Regensburg, numares started with an initial focus on lipoprotein analysis using nuclear magnetic resonance spectroscopy (NMR). Over time, the company's focus extended to metabolomics-based diagnostics. "The space of single biomarkers is limited but combining biomarkers is what we call metabolomic networks," said Maximilian Zucker, CTO at numares. "The idea is that you take mediocre biomarkers and combine them in order to get good performing biomarkers."

The bladder test is being developed to run on the company's AXINON IVD software-based test system which employs NMR to evaluate metabolomic networks. A urine sample is obtained from the patient, an NMR spectrum is created, then evaluated by the test. The company's AXINON system is able to generate data independent of the NMR device or the user, enabling a fully automated analysis of patient samples.

The results are then used to provide information on the disease status of patients. Although NMR is the method of choice to detect metabolomic networks due to its ability to simultaneously quantify many metabolites, in the past it was considered too complex to be used in metabolomics due to technical limitations.


*Maximillian Zucker, numares CTO*


*Philipp Pagel, numares CMO*

Zucker said: "What we have achieved is that we are able to standardize NMR by developing our proprietary Magnetic Group Signaling (MGS) technology that enables NMR for highly standardized testing so it is suitable for diagnostic use. MGS standardizes NMR systems and sample processing to ensure reproducible results on different NMR instruments."

The bladder cancer test will be the second metabolomic network-based diagnostic developed by the company, following its launch of renalTX-SCORE, for the detection of kidney allograft rejection earlier this year.

"Bladder cancer is a pretty common tumor but the symptoms are very unspecific so in a typical situation a patient can present with very non-specific symptoms," said Philipp Pagel, CMO at numares. "Physicians may find blood in the urine which is sometimes visible but in many case it's not visible. As a result, many patients get a cystoscopy which is a very invasive procedure. For a long time, there's been a need for a non-invasive, screening test for bladder cancer so the goal of our project is to develop a test looking for potential biomarkers to detect the early cancer stages."

The company's first step to develop a test involved approaching centers to obtain urine samples from patients with and without bladder cancer. In total, the company evaluated 300 samples which it used to develop algorithms to build a metabolic network that differentiates between bladder cancer and non-cancerous samples. "In order to diagnose something like that you need a whole lot of samples and machine learning technology to actually identify features of the markers that you can combine for the final product," said Pagel.

"After the initial development steps we ended up with a model that integrates different metabolites and our first performance data looked quite promising so we compared it to other tests on the market and found our test performed better than others. Also our test seems to be more robust to things that interfere with competing tests. For example, some tests have problems diagnosing when the patient has microhematuria [traces of blood in the urine sample] which is one of the most common symptoms of bladder cancer."

numares currently has three products on the market. AXINON lipoFIT for NMR-based lipoprotein profiling, insightLP-S50 for lipid composition analysis of lipoprotein subclasses and the renalTX-SCORE, for the detection of kidney allograft rejection. In addition, it is conducting a project to develop a test for liver cancer detection and diagnosis. Earlier this year, it announced a collaboration with the University of Oxford to develop an IVD test to improve therapeutic decision making for patients with multiple sclerosis.

*Published online 07/21/17*

CONTINUED FROM PAGE 1

requirement is no longer necessary because it has already served its purpose.

## DANISH DILEMMA?

Although CMS has not indicated whether it is reviewing any particular clinical trials as part of its reconsideration of the ICD NCD, many commenters appear worried that the agency may restrict coverage of ICDs based on the results of the DANISH trial, published in 2016.

DANISH randomized 1,116 patients with symptomatic systolic heart failure not caused by coronary artery disease to receive an ICD or usual clinical care without an ICD. In both groups, 58% ended up with a cardiac resynchronization (CRT) pacemaker. After a median follow-up, 4.3% of the ICD group and 8.2% of the control group suffered sudden cardiac death, but the overall mortality rates were similar in both groups 21.6% versus 23.4%.

Many commenters argue that this one study should not persuade CMS to limit coverage of ICDs in the primary prevention population. For example, in its comments on the ICD NCD, the Heart Failure Society of America points out that there was a total of 251 deaths and 172 cardiovascular deaths in DANISH, and that while the hazard ratios for these two endpoints both favor the ICD group, neither endpoint was sufficiently powered to show significance at these levels. "DANISH is under-powered, although the trends clearly favor a benefit from ICDs. The results must not be construed as supporting the position that ICDs do not provide benefit to patients with non-ischemic dilated cardiomyopathy."

The American Heart Association concurs. "A change in coverage for ICD use should not be initiated based on the results of [DANISH] as it is a single trial compared to extensive supporting evidence," the AHA argues in its comments. "Even though total mortality was not impacted, sudden cardiac death events were still reduced by 50% in the ICD arm within DANISH over a relatively short-term exposure period." AHA also points out that DANISH did not fully recruit as many patients as it was originally planned for,

and that it preserved statistical power by extending the follow-up period to "collect more events."

"This approach is invariably inadequate to restore statistical power," AHA argues, while noting that a meta-analysis of DANISH found that primary-prevention ICDs are efficacious at reducing all-cause mortality among patients with nonischemic cardiomyopathy. "The data from the DANISH trial, therefore, is insufficient to warrant a change in the national coverage decision."

## NEW EVIDENCE

The Heart Rhythm Society (HRS) and the American College of Cardiology (ACC) collaborated on a detailed recommendation for changes to the ICD coverage policy based on clinical evidence and technological improvements that have emerged since 2005.

HRS and ACC led the development of appropriate use criteria for ICDs and cardiac resynchronization therapy devices published in 2013. They also collaborated with the American Heart Association to write a 2014 expert consensus statement on the use of ICDs patients who are not included or not well represented in clinical trials.

Based on this clinical evidence, ACC and HRS recommend that CMS expand coverage of ICDs to include patients with LVEF of 40% or less demonstrating nonsustained ventricular arrhythmias at least four days post-MI or coronary revascularization procedure who have inducible sustained ventricular tachycardia or ventricular fibrillation at electrophysiological testing and inclusion of patients with New York Heart Association Class IV heart failure who are awaiting heart transplant.

The current policy states that the ICD should not be implanted within 40 days following a myocardial infarction or within 90 days of a coronary intervention or bypass surgery. *(Also see "Only 8 Percent Of Older ICD-Eligible Heart Failure Patients Get An ICD, Study Finds" - Medtech Insight, 26 Jun, 2015.)* This "waiting period" is supported by results from the IRIS and DINAMIT trials, but HRS and ACC recommend creating exceptions to these rules for patients with existing ICDs or pacemakers that require surgical revision for reasons such as battery depletion or device malfunction, patients with sustained ventricular tachycardia, and patients with syncope thought to be due to ventricular tachycardia or ventricular fibrillation. Hospitals implanting ICDs within these 40-day and 90-day waiting period was the key issue behind a long-running Department of Justice investigation and, ultimately, settlements by about 500 hospitals, paying the government a total $273m on allegations of false claims to Medicare for ICD implants. *(Also see "51 More Hospitals Join Federal ICD Settlement" - Medtech Insight, 18 Feb, 2016.)*

HRS and ACC also recommend including magnetic resonance imaging as an acceptable modality for assessing left ventricular function, in addition to echo, angiography or radionuclide scanning, now that US FDA has approved many ICDs as compatible with MRI.

In its comments submitted to CMS in response to the ICD national coverage analysis, **Abbott Laboratories Inc.** – a major player in the ICD market since it acquired St. Jude Medical earlier this year – points out, "Since the implementation of the NCD for ICDs in 2005, significant clinical evidence has been published substantiating improved clinical outcomes with ICD therapy in specific patient populations."

"These guidelines highlight clinical scenarios such as secondary sudden cardiac death prevention, primary sudden cardiac death prevention, generator replacement at elective replacement indicator and consideration of specific comorbidities," Abbott explains.

In its comments to CMS, **Medtronic PLC** recommends that ICDs be "covered consistent with the clinical guidelines and appropriate use criteria." Medtronic points out that the Agency for Healthcare Research and Quality (AHRQ) assessed the evidence for primary prevention of sudden cardiac death in 2013 and concluded, "There is a high strength of evidence that ICD therapy for primary prevention of SCD, versus no ICD therapy, shows benefit with regard to all-cause mortality and SCD in patients with reduced left ventricular ejection fraction and ischemic or nonischemic cardiomyopathy beyond the immediate post-MI or coronary revascularization periods" and that "there is high strength of evidence that in-hospital adverse events are infrequent." Medtronic also points out that the UK's National Institute for Health and Care Excellence reached a similar conclusion in 2014, based on an assessment of data from 12,638 patients in 13 randomized trials.

Medtronic points out that the current ICD coverage policy provides only for coverage and is not specific to non-covered indications or any indications that might be left up to regional Medicare Administrative Contractors. The company suggests that CMS restructure the ICD national coverage policy to be more like its policy on pacemakers (Medicare National Coverage Determinations Manual 20.8.3) by specifying nationally non-covered indications. The company also wants CMS to cover ICDs for non-covered indications if they are part of an FDA-approved investigational device exemption study.

"We urge CMS to refine the NCD with two goals in mind: to simplify the language in order to harmonize coverage with the clinical guidelines and appropriate use criteria, and to minimize administrative burden and simplify program requirements for providers," Medtronic concludes.

The other big player in the US ICD market, **Boston Scientific Corp.**, urges CMS "to preserve coverage for all currently covered patient populations and technologies, and revise the National Coverage Determination to be consistent with current clinical evidence and professional society recommendations," the company argues in a short letter. "The final policy should not limit device choice, and the selection of the most appropriate device should be made by the patient and physician based on needs of the patient."

## HAS THIS CED FINISHED ITS JOB?

The ACC and HRS, among others, argue there is no longer a need to make participation in a national registry a condition of coverage for ICDs.

In their comment on the ICD coverage policy, the Directors of the Duke Center for the Prevention of Sudden Cardiac Death cite their own analyses of data from the national registry, all of which support continuing with the current guideline recom-

mendations to implant ICDs in eligible patients with an LVEF ≤ 35%. Their analyses also showed that primary-prevention ICDs improve survival in patient sub-groups that were underrepresented in the original randomized clinical trials, including women, racial minorities, and patients with multiple comorbidities. The Duke group also points out that evidence supports implanting ICDs for primary prevention in patients over 65, a group that rarely gets them now. *(Also see "Only 8 Percent Of Older ICD-Eligible Heart Failure Patients Get An ICD, Study Finds" - Medtech Insight, 26 Jun, 2015.)*

"Therefore, the questions that CMS intended for the NCDR ICD Registry to address have been largely answered, and the results certainly support the continued use of primary-prevention ICDs in patients with an LVEF ≤ 35% due to ischemic or non-ischemic cardiomyopathy," the Duke investigators argue. "Given that the purpose of the ICD registry has been fulfilled, the registry can continue to exist as a voluntary program that can be used for quality improvement and public reporting."

Device trade association AdvaMed agrees that the registry-participation requirement may no longer be useful. "The American College of Cardiology's National Cardiovascular Data Registry ICD Registry has been in place for over 12 years and has collected data for more than one million patients," the trade group points out in its comments. "It is critical that CMS reassess the rationale for this data-collection requirement in the 2005 NCD and make a determination based on the evidence collected to date under that requirement regarding whether such data collection should be ended."

*Published online 07/21/17*



# Health-Care Location Coding Could Cut Medtech Rebate Errors, Pilot Finds

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Unified location coding could help resolve two-thirds of chargeback and rebate issues in the medical device industry, outcomes from a pilot project conducted by standards organization GS1 US and the Health Care Industry Distributors Association (HIDA) show. The groups have issued two documents, a proof of concept paper and a best practice guide, detailing the effort and results.

GS1's Global Location Number (GLN) system, which lets GS1 US members assign standardized numeric identification codes to specific locations, has been rolled out across a range of industries. The system can be granular enough to assign codes not just to individual buildings, but to specific rooms within a facility. But while it's seen adoption in areas such as the restaurant industry, usage in health care has been slow.

To change that, GS1 US and HIDA joined forces to see how GLN could help the medical device industry resolve rebate and chargeback issues. The problem arises because different providers contract with manufacturers to pay different prices for medical devices and supplies. The distributor pays one price up front, and if the provider's cost is below what the distributor paid, it's up to the distributor to go back to the manufacturer to ask for the additional money back.

> "There's a lot of activity that goes on reconciling a rebate request back to the manufacturer," explains Beth Gibson, GS1 US's senior director of industry development for medical devices.

But if the distributor, the manufacturer and the customer don't have a set code for the ultimate client location, it can be hard for distributors to get the refund they deserve. Historically, each party in a transaction has used its own proprietary system to code locations.

"There's a lot of activity that goes on reconciling a rebate request back to the manufacturer," says Beth Gibson, GS1 US's senior director of industry development for medical devices. "And it's always driven by sales; they have to show the manufacturer, 'I sold 10 cases of this product to hospital X, therefore I need $5,000 back from you.'" And the complications only grow if, as is common, a contract includes different prices for different individual facilities covered under a single contract, she said.

Jeff Girardi, director of industry affairs, HIDA, said his group was drawn into the project due to member concern over the contracting process in health care. "[Contracting] is fragmented; there's so much inefficiency, there's a ton of waste, and it's been like that for decades," he said. "In the past, people tried to see what they could do at one fell swoop, and we decided to focus on manufacturer-distributor communication and see what we could improve there." Working with GS1 US fit into that ongoing initiative, he said.

GLN allows the manufacturer, provider and distributor to all use the same code, which may even let them do away with proprietary systems. Because providers often don't have or need established GS1 US memberships, the group has set aside a bank of prefixes that group purchasing organizations can use to assign GLNs to their clients' locations.

HIDA's Girardi said that standardized location codes, such as GLNs, fill a known need. "Industry knows there needs to be one standard; everyone's just been waiting for the data to be there." One cause

of the delay, he said, has been the lack of regulation to force a standardized system.

"The silver lining with the new [Unique Device Identifier] rule is, it's forced manufacturers to comply with these labeling requirements, so if people are already incentivized to standardize their labels with the [Global Trade Item Number], they're asking why they can't do the same thing for customer location," he said.

### BIG BENEFIT: PRICING ACCURACY

The GLN proof-of-concept pilot program involved five participants: Two device manufacturers, two distributors, and one group purchasing organization. Each participant submitted data that used a proprietary custom identifier. During the trial, using a GLN to identify the customer resolved 31% of rebate discrepancies. An additional 35% could be reconciled with GLN and minor additional effort.

Gibson suspects the remaining 34% could also be resolved with a more thorough use of GLN. "It's the same problem, but it would take a synchronization effort between manufacturers, distributors and providers to get the hierarchy accurate and complete," she said.

While the distributor has the greatest financial interest in GLNs, Gibson also sees benefits for manufacturers. "We know that once the manufacturer and distributor are aligned, the other beneficiary is the provider, because they'll get the right price on their invoice every time," she said. "And invoice error has always been one of the biggest complaints of providers. This would go very far to help provider pricing accuracy, which could be a big distinguishing factor for manufacturers in contracting."

Girardi said GLNs would also save manufacturers as well as distributors money by eliminating inefficiencies, rework, and time lost on payment rejections or disputes.

As a follow-up to the proof of concept, the GS1-HIDA workgroup is developing a quick-start guide for the health-care industry explaining how to implement GLNs in the rebate and chargeback process, Gibson said. The guide is expected by the end of the year.

*Published online 07/17/17*

# Former US Device Center Official Is Now Gottlieb's Chief Of Staff

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Lauren Silvis, who has two years under her belt as a top official in US FDA's device center, is broadening her portfolio. FDA Commissioner Scott Gottlieb officially appointed Silvis as his chief of staff after three months serving in the post on an acting basis.

Prior to taking on the acting chief of staff role in April, Silvis served as deputy center director for policy at the Center for Devices and Radiological Health since May 2015. *(Also see "FDA Device Center Names New Deputy Policy Director" - Medtech Insight, 4 May, 2015.)* Before joining FDA, she was an attorney at Sidley Austin, where she represented both device and drug firms on FDA regulatory matters, including pre-market review, clinical trial and product promotion issues.

At the device center, she helped lead overall development of regulations, guidances, and other policies. She also was the CDRH point-person for several issues relevant to the broader FDA, including FDA-CMS parallel review and off-label communications policies.

"At CDRH, she provided executive leadership on the development and implementation of all policies, regulations and guidance," Gottlieb noted in a memo to agency staff announcing Silvis' appointment. "She has worked regularly with many of you across the agency, especially on key cross-cutting issues."

In the chief-of-staff role, Silvis will have an expansive portfolio in supporting Gottlieb's agenda. Her promotion is part of Gottlieb's ongoing effort, since joining the agency in May, to staff top FDA positions with his preferred team. Earlier this month, he named Rebecca "Becky" Wood as FDA's chief counsel, replacing Elizabeth Dickinson, who will stay on as senior deputy to the chief counsel. Like Silvis, Wood is a former Sidley Austin attorney. *(Also see "US FDA Gets A New Lawyer: Rebecca Wood Named Chief Counsel" - Medtech Insight, 18 Jul, 2017.)*

Gottlieb also recently named new acting personnel for two other top FDA posts – chief scientist and deputy commissioner for global regulatory operations and policy.

At CDRH, Associate Director for Strategy and Regulatory Operations Lauren Roth and Associate Director for Policy Jonette (Joni) Foy are co-covering Silvis' former post on an acting basis.

*Published online 07/19/17*

# US FDA Maturity Model Pilot Program Gets October Meeting Date

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US FDA is convening a workshop at its Maryland headquarters on Oct. 10 to discuss its plans for a pilot project that would use third-party assessors to measure the maturity of a company's manufacturing systems to help shape the agency's regulatory, compliance, and enforcement decisions.

The agency has been working closely with the Medical Device Innovation Consortium to adapt the well-established "Capability Maturity Model Integration" program to the device industry to measure the extent to which companies have adequately developed practices and processes to ensure that quality is pervasive throughout their organization. *(Also see "Gifts For Industry: From Waived Inspections To Pre-Market Leeway, US FDA Woos Firms For Maturity Pilot" - Medtech Insigh, 25 May, 2017.)* FDA is

now looking to launch a voluntary pilot program in 2018 to let companies be assessed under the maturity model by third-party organizations. This experience should help the agency rethink and reprioritize how this information can improve its approach to ensuring product quality.

The Oct. 10 meeting will be an opportunity for potential participants in the pilot and others to weigh in on the details, including the approach to independent maturity assessments, rules of engagement between FDA and companies during the pilot and potential incentives to join the pilot. The agency has previously signaled plans to remove any companies who participate in the pilot from routine facility inspections. Participants might also be able to avoid pre-approval inspections and to interact with FDA about potential quality problems instead of initially receiving a warning letter. Further, maturity assessments could lead firms to be given a break in certain pre-market review steps.

FDA will formally announce the maturity model appraisal framework and implementation plan for the voluntary pilot during the upcoming workshop. Agency officials have said they hope to have maturity model program fully operational by 2020. In addition to the workshop, FDA will accept written comments on the topic through Oct. 18.

*Published online 07/24/17*

# India Consults On 'Essential Principles' Ahead Of New Rules For Devices, IVDs

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The Indian government is seeking feedback on a draft guidance that covers the essential principles medical device- and IVD-makers will need to follow to ensure the safety and performance of their products according to new rules governing medtech that are scheduled to kick in next year.

The 27-page draft document was prepared under the provisions of the forthcoming Medical Devices Rules, which are due to come into effect on Jan. 1, 2018. The new rules mark India's first device-specific regulatory framework.

The draft guidance describes fundamental design and manufacturing requirements that, when met, indicate a medical device or IVD is safe and performs to its specification. It specifies seven general requirements of safety and performance that apply to all devices and IVDs. For example, it says that every medical device requires clinical evidence, appropriate for its intended use and classification, demonstrating that the product complies with the applicable provisions of the essential principles.

There are further design and manufacturing requirements of safety and performance, some of which are relevant to each medical device. The design and manufacturing requirements in the document are grouped within the following categories:

- Chemical, physical and biological properties;
- Infection and microbial contamination;
- Manufacturing and environmental properties;
- Devices incorporating a substance considered to be a medicinal product or drug;
- Devices incorporating materials of biological origin;
- Devices with a diagnostic or measuring function;
- Devices that incorporate software and standalone medical device software;
- Active medical devices and devices connected to them;
- Environmental properties;
- Protection against radiation;
- Protection against mechanical risks;


- Protection against the risks posed to the patient by supplied energy or substances;
- Protection against the risks posed to the patient for devices for self-testing or self-administration or intended by the manufacturer for use by lay persons;
- Information supplied by the manufacturer, i.e., label and instruction for use; and
- Performance evaluation including analytical performance and where appropriate, clinical evaluation.

The draft guidance was produced in consultation with device and IVD industry stakeholders, said Drugs Controller General G.N. Singh. The document clarifies that it does not dictate how a manufacturer should prove that its medical device has met the essential principles, providing flexibility to manufacturers and catering to technological advances and changes in the development of new devices.

The draft document was published on the Central Drugs Standard Control Organization's website this week. It says that stakeholders have three weeks to submit comments in response.

The CDSCO recently published a draft list of more than 700 devices and IVDs clarifying how these products would be classified under the new Medical Devices Rules. India's industry association, AiMeD, subsequently claimed that some of the products on the list had been classified incorrectly. *(Also see "Indian Medtech Finds Errors In New Draft List Classifying Devices, IVDs" - Medtech Insight, 17 Jul, 2017.)* The list is expected to be finalized at least three months before new medical device rules come into effect in January.

*Published online 07/21/17*

## UNLOCKING LEGALITIES:

# Ninth Circuit Allows Wider Range Of False Claim Suits

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A US Supreme Court verdict last fall seemed to significantly raise the bar for False Claims Act convictions. But some legal observers think a Ninth Circuit ruling issued July 7 may signal that courts will accept a broader array of reasoning than expected.


In the 2016 case, *Universal Health Services v. United States ex rel. Escobar*, the high court ruled that companies can only be held liable for FCA violations if they filed Medicare claims that make a specific representation about the good or services provided – and the company's failure to comply with regulations made those representations "misleading half-truths." In addition, the misrepresentation must directly influence the government's decision to pay for the good or service. *(Also see "FCA Liability After Escobar: Challenges And Opportunities For Device Companies" - Medtech Insight, 12 Oct, 2016.)*

But while that *Escobar* standard has been used in several recent court rulings, the Ninth Circuit seemed to step away from it in reviving a *qui tam* case against **Gilead Sciences Inc.**that had previously been dismissed for failure to state a claim. And the court's ruling against Gilead was written broadly enough that it may be applied to device manufacturers in the future, says Anne Walsh, a partner with law firm Hyman, Phelps & McNamara.

"Device manufacturers, like drug manufacturers, will view this ruling as a setback," she said. "They may want to lean on the facts of this case, because it involves a drug and drug manufacturing. But I think no matter what, it is a disappointing ruling from the ninth circuit."

However, she further noted that device manufacturers may be at less risk than drug manufacturers of future false claims cases because of differences in the reimbursement process. The government directly pays for drugs, while devices typically are covered as part of a procedure cost. As a result, the "materiality" analysis is more removed for devices than for drugs.

In the Gilead case, the whistleblowers claimed that Gilead made false statements to FDA about its compliance with HIV drug regulations. The former employees specifically said that Gilead used unapproved ingredients in its drugs and didn't tell FDA about manufacturing issues.

The court found that the whistleblowers had alleged sufficient facts to proceed on three bases. The first was that Gilead made false statements that its drugs were FDA-approved when they were not. "That's about a false statement, and it could apply to a drug or a device," Walsh said. But she noted the specific allegation that Gilead had used an unapproved facility to make some drug components was less likely to apply on the device side, because devices are manufactured differently from drugs.

Secondly, the plaintiffs said that Gilead implied the medications were manufactured in approved facilities and met other regulatory requirements by billing Medicare – another issue that could apply to devices too, Walsh said. The *Escobar* ruling allowed this basis for liability only if the claim made specific representations about the product provided, and the manufacturer failed to disclose its noncompliances. In *Gilead*, the court argued that billing under the drug names implied they met compliance standards.

And finally, the court found that the complaint supported an allegation that Gilead had obtained regulatory approvals for the HIV drugs by misleading FDA about its manufacturing issues, and that the false approvals made every subsequent claim false.

The Ninth Circuit also discarded a lower-court determination that Gilead's alleged fraud was directed at FDA, rather than the Centers for Medicare and Medicaid Services, and so wasn't relevant to the decision to pay the claims.

"Both the FDA and the Center for Medicare & Medicaid Services (CMS) … are overseen by the Secretary of Health and Human Services," the ruling states. "Therefore, the fraud was, at all times, committed against the Department of Health and Human Services. But more importantly, the False Claims Act imposes no such limitation."

The Ninth Circuit said it had decided to allow the case to proceed despite *Escobar* because Gilead was alleged to have actively made false statements by altering inventory codes and shipping and tracking information. In an earlier FCA case that the court had dismissed, there wasn't evidence the defendant had made any specific false statements.

"The court went to great lengths to describe Gilead's conduct differently, because of the specific issue of false statements," Walsh said. "In the earlier Ninth Circuit case, there weren't allegations about false statements, so there the judges felt they could apply *Escobar* to dismiss the case."

In an earlier case directly involving devices, the First Circuit dismissed FCA allegations against device manufacturer ev3 Inc (now part of **Medtronic PLC)** last December. The court said the charges against ev3 didn't meet post-*Escobar* standards, in part, because FDA hadn't taken any action against the alleged false submissions. *(Also see "Appeals Court Rejects False Claims Approach To FDA Off-Label Cases" - Medtech Insight, 23 Jan, 2017.)*

The disparities between the First and Ninth Circuit rulings create the potential for a circuit split, Walsh said, though she's unaware of any efforts to challenge it. She was also unaware of any cases in the pipeline that would more clearly delineate the materiality requirement applicable to medical device manufacturers for FCA liability.

*Published online 07/21/17*

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