

Medtech Insight

Issue 44

medtech.pharmamedtechbi.com



Pharma Intelligence
Informa

May 22, 2017



EU's New Medical Device Regulation: A Timetable To Kickstart Planning

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The EU's Medical Devices and IVD Regulations were published in the Official Journal of the European Union May 5, providing a much better idea of how the deadlines to implement the new regulations will unfold. *Medtech Insight* put together a detailed table laying out key implementation steps and dates to help stakeholders start making plans, line up priorities and argue for the necessary resources.

The majority of deadlines are detailed two sections of the Medical Devices Regulation (MDR): in Article 120, "Transitional provisions" (pages 89 and 90), and Article

123, "Entry into force and date of application" (pages 91 and 92). In the IVD Regulation (IVDR), deadlines are detailed in Article 110, "Transitional provisions" (pages 80 and 81), and Article 113, "Entry into force and date of application" (pages 82 and 83).

Here, we address the MDR deadlines. A separate article will focus specifically on the IVD deadlines, which mirror the MDR approach to a great extent.

Broadly, the Regulations take effect on the 20th day following the May 5 publication and the MDR fully applies three years later, on May 25, 2020, and the IVDR five years later, on May 25, 2022.

While May 5 was the starting point for the implementation schedule, there appears to be a one-day slippage in some later deadlines. But what does a day's difference matter? We will no doubt find out at a later date.

EXPLAINING EU JARGON

The wording in some parts of the MDR articles are full of complicated cross-references. One particularly tricky section is Article 120.8, relating to registration of devices in the new Eudamed device database – specifically how long manufacturers will have to register their devices in the updated database and when notified body must communicate updates relating to manufacturer certificates. The table attempts to tease out the meaning and context of this section, but it may be up to lawyers to establish the dates with certainty. Expect to hear much discussion

CONTINUED ON PAGE 12



VISIT

Go to MedtechInsight.com for a parallel feature addressing deadlines for the EU IVD Regulation, and for an editors' podcast discussion about what companies are up against with the new device and IVD regulations.



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inside:

Cover / EU's New Medical Device Regulation: A Timetable

To Kickstart Planning – The EU's Medical Device and IVD Regulations are published in the Official Journal of the European Union, setting a series of deadlines for implementation and compliance. There is a lot to do in a relatively short amount of time. Here's a timetable of what to expect.

EDITORS' PICK

5 **User-Fee Facts: 10 Key Medtech Details From US**

FDA Agreements – While Congress makes its push to reauthorize US FDA user fees by mid-summer, here are 10 important details from the underlying industry-agency user-fee agreements that medtech firms should know.

POLICY & REGULATION

8 **With Gottlieb Sworn In, His Focus Should Be On Quick**

User-Fee Passage, Industry Advocates Say – Scott Gottlieb was sworn in as US FDA commissioner May 11. Device-industry lobbyists say championing quick passage of user-fee reauthorization should be his near-term priority. Gottlieb is a well-known figure by some in industry, including AdvaMed chief Scott Whitaker, who served with him at HHS during the George W. Bush administration.

10 **"Perfect Storm" Arrives: Clock Ticking For Device Firms**

To Conform To ISO 13485, MDSAP, EU & ASEAN Regs – Device manufacturers that haven't begun conforming to various ongoing international regulatory changes are behind the 8-ball and risk noncompliance, industry insider Kim Trautman says.

COMMERCIAL

15 **Wising Up On Intelligence Gathering To Win Medtech**

Tenders – Tenders and large contracts have become an important driver of health-care cost containment, resulting in fewer and more complex transactions, increasing price pressure and ultimately increasing commercial risks for companies selling health-care products. In this guest column, Omar Ahmad and Carlos Meca, of the strategy and

Medtech insight

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marketing consulting firm Simon-Kucher & Partners, discuss how an efficient and comprehensive tender intelligence approach supported by the right tools is one of the key weapons to fight this emerging challenge.

COMPANIES

- 18 J&J Heading Into Fourth Pelvic Mesh Bellwether** – The Philadelphia trial is getting underway just days after a jury handed down a \$20m verdict against the company in the third bellwether case.
- 19 Device Exec Pleads Guilty To Trade Secret Theft** – Christopher Barry, a former VP of R&D at Bard subsidiary Lutonix, pleaded guilty to one count of theft of trade secrets. He now faces up to two and a half years in prison.
- 19 Senseonics, TypeZero Join Forces On Artificial Pancreas** – Diabetes companies Senseonics and TypeZero Technologies have signed a research and development licensing agreement to develop an artificial pancreas.
- 20 BioTrinity 2017: Gut Potential, Drug Delivery Innovations And Partnering Opps** – Industry experts, investors and start-ups from across the pharma, biotech and medtech sectors gathered at the annual BioTrinity conference in London to explore partnering and investment opportunities, as well as future trends in the health-care industry. *Medtech Insight* spoke to VC firm Seventure on the growing buzz around microbiome and how life-sciences companies can capitalize on opportunities in this field, and took a closer look at two companies with very different drug delivery approaches. This article also includes a roundup of the early-stage medtech companies showcasing their technologies at the meeting.

R&D

- 22 HRS 2017: Medtronic And Boston Scientific's Less-Invasive CRM Devices Perform As Hoped In Real-World Registries** – Results from the post-approval trials of Medtronic's *Micra* Transcatheter Pacing System and Boston Scientific's *S-ICD* presented at the Heart Rhythm Society Scientific Sessions in Chicago show these "leadless" devices can be implanted in "real world" patients with acute outcomes similar to those of the pre-market trials that had more restrictive inclusion criteria.

USER-FEE FACTS:

10 Key Medtech Details From US FDA Agreements

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US FDA user-fee reauthorization legislation is proceeding through Congress, most recently with a May 11 markup in the Senate Health, Education, Labor and Pensions Committee, and lawmakers want a bill passed by July.

But it has already been almost nine months since FDA and industry trade groups completed negotiations on the underlying agreement that forms the basis of the reauthorization legislation. (Also see “Industry, US FDA Strike \$1Bn Deal After Contentious User-Fee Negotiations” - *Medtech Insight*, 23 Aug, 2016.) Since then, there has been a political earthquake in the US with the election of Donald Trump to the White House, an often-chaotic legislative environment and, in the realm of medtech, a rollout of about a dozen separate bills to reform everything from facility inspections to lab-test and imaging equipment oversight, to hearing-aid access. (Also see “Bill Bonanza: US Congress Sprouts Medtech Legislation This Spring” - *Medtech Insight*, 2 May, 2017.)

In that mix, it's easy to lose sight of the core details of the user-fee reauthorization agreements, which will have a significant impact on companies' day-to-day regulatory operations in the fiscal year 2018-2022 period. Those changes are captured partially in the user-fee bill moving through Congress, and partially in the FDA commitment letter that details everything the agency will do with its extra user-fee cash that does not require a formal statutory change.

Here are 10 key points about the underlying user-fee agreements that might not be highlighted in ongoing congressional hearings, but have important implications for device and diagnostics firms.

1. YOU'LL PAY MORE...*

***(Especially for 510(k) submissions, if your firm earns more than \$100m in annual revenue)**

Device industry groups tout the MDUFA IV user-fee agreement as a good bang for a company's buck, raising an additional

\$320.5m (plus inflation) in user fees above the MDUFA III baseline. But that money has to come from somewhere, and the primary source will be increased submission and registration fee rates. Under the agreement moving through Congress, the year-to-year impact will be felt most dramatically by device firms in the first year of the program, FY 2018 (starting Oct. 1). The increase will be particularly sharp because FDA was forced to reduce FY 2017 rates as a result of prior-year over-collections. (Also see “US Device User-Fee Rates Will Drop About 10.3% In Fiscal 2017” - *Medtech Insight*, 1 Aug, 2016.)

Thus, the pre-inflation fee for submitting an original PMA will jump about 25% to \$294,000 in FY 2018 (or \$73,500 for firms that report \$100m or less in annual revenue), and the annual establishment registration fee for all companies will jump about 47% to \$4,978 from the FY 2017 value. But the biggest change will be for 510(k)s, the most common pre-market submission type. Due to a calculation change included in the agreement, the standard fee for 510(k) submissions will more than double, increasing from the FY 2017 rate of \$4,690 to \$9,996 in FY 2018. The impact will not, however, be as dramatic for smaller firms that earn \$100m or less, because small businesses will now pay only one-quarter, rather than one-half, of the standard rate for 510(k)s. Qualifying firms will pay \$2,499, which is only a \$154 increase from FY 2017, and actually less than the FY 2016 small-business 510(k) rate. Fee rates will incrementally increase on an annual basis, by a total 11.5% between FY 2018 and FY 2022.

2. ...AND THERE IS NO OVER-COLLECTION REDUCTION DOWN THE ROAD

An important change in the agreement that FDA fought to include would get rid of prior user-fee-program provisions that required the agency to offset prior-year over-collections with fee reductions in the fifth and final year of a cycle (which was the cause of the FY 2017 rate drop). Going forward, “If the collections are in excess of the resources needed to meet performance goals given the workload, or in excess of inflation-adjusted statutory revenue targets, FDA and industry will work together to assess how best to utilize those resources,” the commitment letter states.

On the other hand, if submission or registration volumes drop below projections, it is possible that base-fee amounts would need to be increased to make up the revenue.

3. DE NOVOS' TIME TO SHINE?

FDA is also adding one completely new fee category. Assuming the MDUFA IV agreement is approved, companies will have to, for the first time, pay a fee when submitting a *de novo* classification, which will be set at 30% of the PMA fee. (In FY 2018, the pre-inflation rate would be \$88,200.) The new fee reflects growing

Dollars And Cents

- The 510(k) submission fee rate will increase from 2% to 3.4% of the base PMA fee rate, but small businesses will only have to pay one-quarter of the standard 510(k) fee, rather than the 50% rate in MDUFA III.
- The new *de novo* classification fee will be set at 30% of the PMA rate.
- The base user-fee rates will be adjusted for inflation, and can also conceivably be increased to meet revenue targets if submissions/registrations are below projections.
- User-fee rates cannot be reduced as a result of prior-year over-collections.

use by companies of the *de novo* pathway, which offers a route to market for novel, but low-to moderate-risk devices, and FDA is concerned that it won't be able to keep up with the demand without targeted resources. The fee is linked to first-time FDA performance goals for *de novo* reviews – setting a 150 “FDA-day” review standard (not including time when a submission has been sent back for response by the sponsor), which the agency commits to meet half the time for FY 2018 submissions, and will ramp up to 70% performance by the time it gets to the FY 2022 cohort.

4. ALL E-SUBMISSIONS, ALL THE TIME?

The MDUFA IV agreement sets the groundwork for moving from what remains still a largely paper-based FDA device submissions process to an electronic one. That has big implications for improving the consistency and completeness of industry submissions, the FDA review of those submissions, and the agency's ability to track and audit its review process. (Also see “FDA Tries To Get ‘Smart’ In Standardizing 510(k) Reviews” - *Medtech Insight*, 4 Nov, 2015.)

While companies must currently submit an “e-Copy” (e.g., a CD version) along with paper submissions, the device center is still in piloting stages for employing an actual electronic submission platform that companies can routinely use for pre-market submissions. The user-fee bill grants FDA authority to require all submissions, including pre-submissions, 510(k)s, PMAs and others, be submitted solely in electronic format by an FDA-designated date after the standards for an electronic template has been established in a final guidance. FDA would have until October 2020 to finalize guidance setting out such standards.

5. LESSONS FROM DECENTRALIZED EU APPROACH?

By no measure does this user-fee deal pass off FDA's centralized review responsibilities to outside groups, but there are several provisions in the agreement that could spark a bigger role for accredited third-parties in medtech firm's path to market; that is, more in the direction of the role of notified bodies in the EU. And, along with the electronic submissions sections mentioned above, these approaches might support a more globally harmo-

nized pre-market process in the years to come. (Also see “Single Marketing Application Review For Multiple Jurisdictions On Horizon” - *Medtech Insight*, 6 Apr, 2017.)

There are two parts of the agreement worth highlighting, in particular, on this theme. One is new authority for FDA to establish a conformity assessment scheme, in which accredited “testing laboratories” will be designated to review, in FDA's stead, a company's conformance to recognized consensus standards used to help support/streamline a firm's pre-market submissions. FDA says it will trust the laboratory rather than engage in conformance-standard scrutiny of its own during pre-market reviews. (Also see “Device Standards Provision In Cures Bill Could Speed Up 510(k) Clearances” - *Medtech Insight*, 1 Dec, 2016.)

The other relevant provision addresses planned efforts to revitalize FDA's long-running, but lightly used third-party 510(k) review program. The user-fee reauthorization bill would give the agency more flexibility to make decisions on what devices should be eligible seeking 510(k) review by an accredited third party rather than FDA. Under the agreement, the agency will also establish a plan to cut down on its need to “re-review” third-party assessments, which can eat up a lot of time, and clearer standards for accrediting, training, suspending and auditing the third parties.

6. PERFORMANCE GOALS: SHARED OUTCOMES, PROCESS PRECISION

Another point-of-interest in the latest user-fee agreement: For the first time, FDA and industry did not adjust measures for the core performance goal categories that have been with the device user-fee program since it began about 15 years ago: the

Select New MDUFA IV Performance Goals

CATEGORY	GOAL DESCRIPTION
PMA – Shared Outcome Goal	A ramp-down in three-year total-time-to-decision averages, from 320 days for the FY 2016-2018 receipt cohort, to 290 days for the FY 2020 to FY 2022 cohort.
510(k)s – Shared Outcome Goal	A ramp-down from 124 total days for FY 2018, to 108 days for FY 2022.
Pre-submissions	FDA will provide written feedback to a pre-submissions request within 70 days of receipt or five days before a meeting, whichever comes first. The goal will be reached for 1,530 submissions in FY 2018, and ramp up to 1,950 in FY 2022.
<i>De novo</i> Classifications	150 “FDA-day” review standard for 50% of submissions in FY 2018, incrementally increasing to 70% performance in FY 2022.
CLIA Waivers	A 180 FDA-day standard for 90% of dual 510(k)/CLIA waiver submissions; a 150 FDA-day standard for 90% of CLIA waiver by applications without an advisory panel meeting; a 320 FDA-day standard for 90% of CLIA waiver by applications with an advisory panel meeting.

number of "FDA days" to complete PMA, PMA supplement and 510(k) reviews. Those goals will remain unchanged from the FY 2017 MDUFA III levels for the next five years, as will the in-review-process "substantive interaction" goals that were previously established in the program.

What is changing? For one, FDA and companies are committing to more reductions in so-called "shared outcome goals," which count the time an application spends in both the agency's and the sponsor's hands. Also, a few more in-process goals are being added to more precisely target potential trouble spots of a review. In particular, FDA has agreed to issue a PMA decision within 60 days of an advisory committee meeting being held on the application, and to issue a PMA decision within 60 days of a sponsor responding to an FDA "approvable" letter.

Two areas that will get enhanced end-process performance goals are pre-submissions and CLIA waiver reviews. Even so, no user fees have been linked directly with either of these submission types.

7. GUIDANCE DOCUMENTS

FDA has committed to producing four completely new guidance documents in the user-fee agreement, on: *de novo* reviews, electronic submissions, a new accreditation scheme to streamline FDA's reliance on consensus standards and the third-party 510(k) review program. Meanwhile, the agency agreed to specific revisions to five existing guidance and to finalize one draft guidance, on software modifications. (Also see "Must-Do Guidance Development: What's On Tap From Cures, MDUFA IV" - *Medtech Insight*, 22 Dec, 2016.)

8. DIGITAL HEALTH DIVISION

Part of the MDUFA IV user-fee funds will be supporting FDA's efforts to stay on top of digital-health developments, specifically as the agency defines it, both "software as a medical device" (SaMD) products and "software inside of medical devices" (SiMD). The upshot of that funding, according to the commitment letter, will be a new central digital health unit within CDRH's Office of the Center Director, with the charge to "ensure proper coordination and consistency" digital-health reviews across the agency. In addition, FDA says it will put special attention to establishing novel pre-market pathways for digital devices and engaging in international harmonization efforts on the issue.

One important piece of context: since FDA and industry signed on to the MDUFA IV agreement last August, Congress pass provisions in the 21st Century Cures Act that remove several categories of software products from the agency's authority. (Also see "'Cures' Bill Circumvents FDA On Medical Software Regs" - *Medtech Insight*, 30 Nov, 2016.) That will certainly have some implications for how the device center rolls out its digital-health plans, although the agency says it still plans to implement a system of surveillance for the exempted software products or functions. (Also see "FDA 'Cures' Fund Breakdown: Breakthrough Devices, HDEs, IRB Flexibility And More" - *Medtech Insight*, 9 May, 2017.)

9. SUMMARY MALFUNCTION REPORTS

FDA agreed in the deal to allow more device malfunctions ("for most, if not all, device procodes") to be reported by companies on a quarterly basis, in summary form, rather than individually and in real-time. There are exceptions, of course, including the need to report a new, previously unknown type of malfunction for a device individually, but the change could significantly streamline companies' Medical Device Reporting responsibilities. This commitment is included in FDA's letter under the "Real World Evidence" heading, pointing to, perhaps, its primary purpose for FDA: summary versus individual malfunction reports can provide the agency with a more comprehensive picture of how a device is actually performing in clinical practice. (Also see "MDR Reporting: FDA Embraces Adverse Event Summaries Under MDUFA IV, But Flouts Similar FDAAA Mandate" - *Medtech Insight*, 5 Jan, 2017.)

10. COMBINATION PRODUCTS

And it's not just the MDUFA agreement that device firms should heed. The Prescription Drug User Fee Act (PDUFA VI) includes provisions targeting combination products that are important for some medtech players. In a rare move, the PDUFA deal will send some funds directly to the device center as part of an overall plan to streamline combination-product reviews, adding on to other efforts from Congress and FDA to improve what are widely recognized inefficient processes for certain products that include a device, and drug or biologic. (Also see "PDUFA First: Fees To Support US FDA Device Center Staff" - *Medtech Insight*, 25 Aug, 2016.) ▶

Published online 05/11/17

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With Gottlieb Sworn In, His Focus Should Be On Quick User-Fee Passage, Industry Advocates Say

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Scott Gottlieb was sworn in as the 23rd commissioner of FDA May 11, and device industry groups are hoping he hits the ground running in advocating for quick passage in Congress of user-fee reauthorization and FDA reform legislation.

The bill includes the MDUFA IV agreement reached last summer to increase industry fees in return for enhanced performance and investments in the US FDA pre-market review process. It advanced through the Senate Health, Education, Labor and Pensions Committee on the same day Gottlieb was sworn in, and it has also made progress in the House. (Also see *"User-Fee Bill Advances With Broad Support, Additional Device Reforms"* - Medtech Insight, 11 May, 2017.)

But the Trump administration has given mixed signals about the plan, which was negotiated during Barack Obama's term. The White House issued a budget proposal in March that asked for a substantial increase in user fees, beyond what industry agreed to, and a big drop in appropriations for FDA, an idea lawmakers have so far ignored. (Also see *"Trump Budget: FDA-Regulated Firms Should Pay 'Their Share' In User Fees"* - Medtech Insight, 16 Mar, 2017.) Now that Gottlieb, a physician, think-tanker, venture capitalist and former top official at FDA, is in place, lobbyists from AdvaMed and the Medical Technology & Imaging Alliance (MITA) hope the tone from the administration will change.

"I don't see him stepping in and taking an active role in renegotiating anything, but when the time is right, I think he'll step in to support the agreement as it is currently constructed, and perhaps also support some of the additional riders that we're working on in the legislative process," said Scott Whitaker, president and CEO of AdvaMed, in an interview.

The user fee bill, Whitaker says, is core to everything the device industry does and provisions in the bill, especially dealing with reduc-

ing review times while adding clarity and transparency to the process, are particularly important. "From the broad perspective, I think Scott understands that and will be focused on it," Whitaker said.

Among the provisions in the deal are better submission tracking tools, more resources for FDA, including new staff, and tighter review deadlines, among a range of other reforms and investments. (Also see *"User-Fee Facts: 10 Key Medtech Details From US FDA Agreements"* - Medtech Insight, 11 May, 2017.) If reauthorization is not approved by July, layoff notices will need to go out to some FDA staff.

GOTTLIEB AND ADVAMED CHIEF: FORMER HHS COLLEAGUES

Whitaker had a working relationship with Gottlieb when both of them served at the US Department of Health and Human Services during the George W. Bush Administration. Whitaker served as HHS chief of staff during a period when Gottlieb was a top official in the FDA commissioner's office, and also served a short stint at CMS. (Also see *"Gottlieb At FDA: Industry Will Look For User-Fee Deal Support, Restrained Regulations"* - Medtech Insight, 10 Mar, 2017.)

"He's just a really, really bright guy and, from my perspective, brings the right approach to government service and an agency like the FDA," Whitaker said.

As not just a former FDA official, but also as a physician and a cancer survivor, Whitaker says Gottlieb will likely bring a set of unique experiences that the agency needs and will also be an asset to the medical device industry. He also says the appointment of Gottlieb, a formal FDA official, will be a morale booster for agency staffers.

But, at the same time, Gottlieb's confirmation in the Senate was more partisan than typical FDA commissioner votes. (Also see *"Gottlieb Becomes FDA Commissioner With Immediate Issues Pending"* - Medtech Insight, 10 May, 2017.) Some lawmakers argued Gottlieb is too close to the industry and that, due to his work as a venture capitalist and investor, he has troubling financial ties to medical product companies. (Also see *"FDA Nominee Gottlieb's Recusals Span Clinical Decision Software Firms, Imaging Centers, Drug Makers"* - Medtech Insight, 4 Apr, 2017.) Whitaker argues that characterization is unfair.

"Scott is his own man, and he's got his own ideas," said Whitaker. "What we're encouraged about and what we think is important, is you want an FDA commissioner who understands how the industry works and the important role the industry plays in treatments and cures of patients who are suffering, and I think Scott brings that perspective.

"But to suggest Scott would somehow be beholden to industry that would be a big mistake," the AdvaMed head said. "He's an independent-minded guy, a very thoughtful guy and we hope he agrees with us on some of the issues; I don't expect he always will, but that's fine," Whitaker added. "That's what you want from an FDA commissioner."

While Gottlieb will also spend a lot of time on issues important to other industries regulated by FDA, such as drugs and food, Whitaker says he expects the new commissioner will be very accessible, and will likely reach out to himself and to AdvaMed's board to learn about the issues impacting the device industry.

Whitaker started his HHS career as assistant secretary, a post that required him to work through about a dozen Senate confirmation hearings for officials at the department. That gave him a unique perspective on the challenges candidates have to go through during the confirmation process, and, he said, it's knowledge that he says he imparted on the new FDA commissioner.

"I've talked to him off and on throughout the confirmation process and mostly just trying to help give him a sense of what that's like," said Whitaker.

IMAGING CONNECTIONS NOT AS STRONG

While some lobby groups have more direct experience with Gottlieb, because of various issues they've intersected on, that's not so much the case with MITA.

"I know him based on what I've read in the media," said Patrick Hope, MITA's executive director, when asked about his experience with Gottlieb. "A lot of his background is in pharma and some in devices, but not a lot in imaging, and that might be why we haven't interacted as much."

After championing the user-fee reauthorization bill, MITA's second priority for Gottlieb is to push for FDA to regulate third-party servicing of medical imaging devices. While the group has been lobbying the agency on the since the late 1990's, according to Hope, their efforts have become more critical in recent years as more complex machines are now on the market that require servicing, and hospitals often contract with organizations other than the manufacturer to perform maintenance.

FDA currently only regulates servicing performed by manufacturers. MITA says they want to see a more even-handed approach, where the agency regulates servicing of imaging devices regardless of who is doing the servicing.

"What we're seeing is more examples of work that is not being performed at the highest standards. We're seeing more and more of these examples where servicers are using tape [to patch things], safety mechanisms being overridden, the devices are not being properly cleaned and just not being properly serviced," Hope said.

"One of the things about the servicing issue that can't be emphasized enough is this is about patient safety first and foremost and that is why we are so adamant that the FDA engage on this issue," he added.

After Gottlieb has settled into his new role, Hope says MITA plans to set up a meeting to discuss their priorities with him, though they have not yet reached out to the agency to schedule one. The group wants to take the opportunity to educate the new commissioner on the issues affecting medical imaging companies.

"It might be a surprise to him that not everyone who services devices are regulated," said Hope. "It is a blind spot for FDA and it



Scott Gottlieb

is important for the commissioner to be briefed on the importance of this issue."

USER-FEE RIDER PRIORITIES

The group has been successful recently in getting attention to the issue in Congress, and is hoping to get legislation added to the user-fee bill that would require oversight of third-party servicers. In the House, Reps. Ryan Costello, R-Pa., and Scott Peters, D-Cali., have introduced the "Ensuring Patient Safety through Accountable Medical Device Servicing" (H.R. 2118),

which lawmakers signaled would be added to a House user-fee bill. (Also see "House To Link Inspections, 3rd-Party Servicer, OTC Hearing Aid Bills To User-Fee Train" - *Medtech Insight*, 5 May, 2017.) But such a provision was not included in the Senate version of the bill that passed through the HELP Committee May 11.

MITA is hoping the provision, also supported by AdvaMed, will ultimately reach the finish line, potentially with Gottlieb's help.

The third-party servicing provision is one of multiple riders that industry groups are pushing for inclusion in the must-pass user-fee package. Other high-priority provisions would streamline risk-classification of medical device accessories and improve transparency of device facility inspections. Both of those AdvaMed-favored measures *did* make it into the Senate Committee-approved bill.

"There's a lot of frustration around [the inspection] issue with companies, not because we don't want a robust inspection process; we just want it to be predictable so we can move through it smoothly," Whitaker said. "It's in everybody's interest that we do that."

Whitaker says he's confident Gottlieb can be relied upon to help push those bills across the finish line too if the need arises.

DIGITAL HEALTH AND PERSONALIZED MEDICINE

In the long term, Whitaker says he hopes Gottlieb helps ensure a vibrant innovation environment for digital health technologies. The field is already making huge shifts in the industry and AdvaMed has made the issue a priority this year. (Also see "IBM Digs Deeper Roots In Medtech, As AdvaMed Builds Digital Footprint" - *Medtech Insight*, 13 Jan, 2017.)

"Helping navigate [digital health], in such a way that some of the newer and innovative treatments get to patients sooner, is going to be important to us," he said.

Meanwhile, with the Personalized Medicine Coalition wants to make personalized medicine a priority for Gottlieb.

"Scott Gottlieb takes over at FDA at a time when personalized medicines, which represented just 5 percent of FDA's new drug approvals in 2005, now account for nearly one of every four drugs the agency approves," added Edward Abrahams, President of PMC. "FDA helped facilitate this progress by encouraging the development of targeted therapeutics. By building on these efforts, FDA can help continue to ensure the availability of safe and effective medicines that improve patient outcomes and help make the health system more efficient." ▶

Published online 05/11/17

'Perfect Storm' Arrives: Clock Ticking For Device Firms To Conform To ISO 13485, MDSAP, EU & ASEAN Regs

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Medical device manufacturers that haven't begun conforming to various ongoing international regulatory changes are already behind the 8-ball and are at risk of falling out of compliance when deadlines arrive, a longtime industry expert says.

"Not only does industry have the new ISO 13485 hitting it, but industry also has MDSAP hitting it for, at a minimum, product entry into Canada. Then there are all of the issues that go along with the new EU MDR and IVDR regulations. And ASEAN countries have a 2020 deadline for its Medical Device Directive," said Kim Trautman, a former US FDA international quality systems and regulatory expert.

Companies must become certified to the 2016 version of international quality standard ISO 13485 – which went into effect early last year – by March 1, 2019. (See Figure 1, Timeline 1.) And firms must be audited to the International Medical Device Regulators Forum's Medical Device Single Audit Program (MDSAP) by Jan. 1, 2019, if they want to sell product in Canada. (See Figure 1, Timeline 2.)

Throw into the mix the EU's Medical Devices Regulation, which firms will have to

comply with fully by May 25, 2020, and MDD requirements from the Association of South-east Asian Nations (ASEAN), which take effect on Jan. 1, 2020, and industry is facing a "perfect storm" of regulatory convergence, Trautman says. (Also see "Asia Reg Roundup: Malaysia, Vietnam & India Speed Ahead In 2017" - *Medtech Insight*, 3 Mar, 2017.)

"This is the perfect storm, folks, because it's happening both from the auditing organization perspective, as well as the manufacturer's perspective," she said.

And if things weren't complicated enough already, the EU's IVD Regulation will become fully applicable beginning May 25, 2022.

To meet those timeframes, firms must start work now, said Trautman, who is currently executive VP of international regulatory compliance services at NSF International, working in the consulting firm's medical devices group within its global health sciences division. She left FDA in January 2016 after more than three decades at the agency.

"I can't emphasize enough: There are so many things that are telling you to prepare now," she said May 4 at MedCon 2017 in Cincinnati. "For ISO 13485 and MDSAP,

if you haven't read them, if you haven't done a gap analysis for each, then do it this weekend. You better pull several all-nighters and do it ASAP because it's not simple. This is not simple at all."

MDSAP, created by the International Medical Device Regulators Forum, allows firms to undergo one audit by an accredited third party to satisfy quality regulations for the US, Canada, Brazil, Japan and Australia.

Meanwhile, companies use ISO 13485 to ensure quality systems compliance with regulators in different countries, including Canada, Japan, Australia and the 28 member-states of the European Union. The standard's requirements for device manufacturers are similar – but not identical – to FDA's Quality System Regulation.

Domestic manufacturers must comply only with the QSR if they plan to sell their products exclusively in the US. However, if a firm plans to market internationally, then it must meet the requirements of both the FDA regulation and ISO 13485.

DON'T BE 'FOOLED' BY ISO DEADLINE

Trautman urged manufacturers not to be "fooled" by ISO 13485's three-year transition window. "The first year is already gone. We are now in the second year. It is highly discouraged to have a new certification or recertification to the old 2003 version," she said.

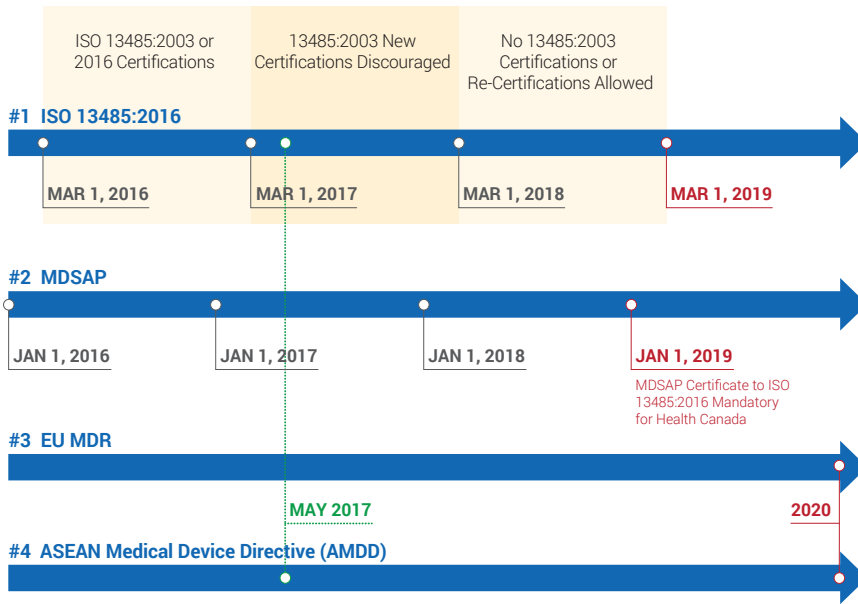
"Unfortunately, I am finding out that many [firms] are deciding to do that anyway, which I would say is probably not the best decision," she said. "Now is the time when you want to be trying these new requirements; you want to be building these new requirements."

"Even though the three-year transition was built to not have a firestorm, the firestorm is already happening."

Trautman was intimately involved in the redo of ISO 13485 as part of the ISO group tasked with revising the standard,

FIGURE 1

Regulatory Deadlines, 2016-2020



Source: NSF International

Technical Committee 210, Working Group 1 (TC210/WG1). She also is chair of IM-DRF’s MDSAP working group.

“I have encouraged many firms to become certified to the 2016 version as soon as possible,” Trautman said of ISO 13485. “Everybody is learning. The auditors are learning. You’re learning. The more the auditors get good at this, they’re tougher they’re going to be on you. ... hint, hint. So, take advantage of this learning curve.”

After March 1, 2018, no new certificates to the 2003 version of ISO 13485 will be issued.

“Now, let’s start putting this together,” Trautman said. “When Health Canada made the decision to set Jan. 1, 2019, as a deadline for using MDSAP [in lieu of its traditional Canadian Medical Devices Conformity Assessment System (CMD-CAS) audits], it was working very, very hard to try to line it up with the predicted publishing of ISO 13485:2016.”

The International Organization for Standardization (ISO) “told us that the new standard would be published within the first quarter of 2016. So, in December 2015, Health Canada said, ‘OK, January 2019 will be our deadline,’” she said. Health Canada

and IMDRF “didn’t have a crystal ball in Geneva [where ISO is headquartered] to know that ISO 13485 wasn’t going to be published until March 1, 2016.”

That means device-makers marketing product in Canada lost, from the get-go, three months to become certified to ISO 13485, because MDSAP – required by Health Canada beginning Jan. 1, 2019 – requires compliance to the standard.

“You’re not going to be able to count on Health Canada moving that Jan. 1, 2019, date. Honestly, if Health Canada does move it, the likelihood is that it’s only going to move the deadline to March 1, 2019, because everybody’s going to need a new ISO 13485 certificate then anyway,” Trautman said.

SELLING IN CANADA? HAVE MDSAP AUDIT BY SEPTEMBER 2018

Firms selling devices in Canada are encouraged to undergo an MDSAP audit no later than September 2018.

That’s “because you have to plan the time of the audit, and plan for work time, assuming there is going to be nonconformances; and allow time for decisions back and forth, or responses back and forth,” Trautman said. “By the time the auditing organization

writes up the report, finalizes your responses and actually hands you that certificate, that’s typically a two- to three-month period of time. Then, you’re running up against the Thanksgiving and Christmas holidays.”

The bottom line? Manufacturers – if they are planning to be in the Canadian market – must be certified to ISO 13485 before an MDSAP audit occurs, which should happen a full three months before the Jan. 1, 2019, Health Canada MDSAP deadline goes into effect.

WORK WITH AUDITING ORGANIZATIONS NOW

But ensuring compliance won’t be easy on already-stressed independent auditing organizations.

“I have clients who have sat down with their auditing organizations and have planned every single recertification and surveillance audit ... between now and 2021 because the auditing organizations are already stretched,” Trautman said. “They’ve been stretched by the unannounced audits from the EU system.”

A 2013 European Commission Recommendation on audits and assessments carried out by notified bodies says unannounced audits should be carried out “at least once every third year” – and more often for high-risk products if the devices are frequently noncompliant or if there are specific reasons to suspect nonconformities. Daniel Shoukier, lead auditor at notified body SQS in Switzerland, told *Medtech Insight* in February that unannounced audits are, indeed, a drain on AO resources. (Also see “An Auditor’s Take: Unrealistic EU Demands Are Causing Notified Body Exodus, Potential Company Collapses” - *Medtech Insight*, 13 Feb, 2017.)

“If they don’t have the resources to take on a new client, they won’t,” Trautman said of the auditing organizations.

“So, if you think you’re just going to change notified bodies in the next couple of years, you may be sadly mistaken, because you best make sure you have another notified body willing to take your work up before you lose the one that you currently have,” she said. ▶

Published online 05/11/17

CONTINUED FROM PAGE 1

around this point as MDR implementation moves forward.

Medtech Insight's table (on pages 12-14) presents MDR deadlines and transitional arrangements under topical headings intended to improve clarity. ▶

Published online 05/09/17

THE HEADINGS:

- Headline dates
- Notified bodies
- Certificates granted under directives: Auditing and CE certificate validity timelines
- Certificates granted under directives: Placing devices on market and putting into service
- Eudamed and UDI
- UDI-specific issues
- Special-case devices
- Governance

EU MDR: An Implementation Timetable

HEADLINE DATES		
When will the Medical Devices Regulation take effect?	20 days after publication of MDR in the Official Journal of the EU	May 25, 2017
When will the IVD Regulation take effect?	20 days after publication of IVDR in the OJEU	May 25, 2017
When will the MDR become fully applicable? (Article 123.2)	Three years after publication of MDR in the OJEU	May 26, 2020
When will the IVDR become fully applicable?	Five years after publication of MDR in the OJEU	May 26, 2022
Can products be placed on the market under the MDR before its full application? (Article 120.5)	Devices that comply with the MDR may be placed on the market before its date of application	This means before May 26, 2020 .
NOTIFIED BODIES		
How soon can notified bodies apply to be designated against the MDR? (Article 123, 3a)	The MDR articles related to notified bodies, Articles 35-50, will apply beginning November 26, 2017 , which is six months after the MDR takes effect. This is when notified bodies can apply to be designated against the new regulations.	Between November 26, 2017, and May 26 2020, the obligations under those articles will only apply to those bodies that have submitted an application for designation under the MDR.
When do notified body designations under the legacy Medical Devices Directive become void? (Article 120.1)		May 26, 2020
Can notified bodies be designated and notified prior to May 26, 2020? (Article 120.6)		Yes, and they can carry out conformity assessment procedures under the new regulation and issue certificates also prior to May 26, 2020.
CERTIFICATES GRANTED UNDER DIRECTIVES: AUDITING AND CE CERTIFICATE VALIDITY TIMELINE		
Can devices still be audited against the MDD/ AIMD after the regulation enters into force on May 25, 2017?		Yes
How long will CE marking certificates issued by notified bodies under the MDD and AIMDD <u>prior to the MDR taking effect</u> on May 25, 2017, remain valid? (Article 120.2)	Certificates issued by notified bodies under MDD and AIMDD, up until May 25 2017, when the MDR takes effect, will be valid until the end of the period on the certificate.	But companies whose products have conformity assessment certificates issued under Annex IV of either directive will become void at the latest on May 27, 2022 .
How long will CE marking certificates issued by notified bodies under the MDD and AIMDD <u>after the MDR takes effect</u> on May 25, 2017, remain valid? (Article 120.2)	They will remain valid until the end of the period indicated on the certificate, which shall not exceed five years from the date the certificate is issued	Certificates will be void at the latest by May 27, 2024 .

CERTIFICATES GRANTED UNDER DIRECTIVES: PLACING DEVICES ON MARKET AND PUTTING INTO SERVICE		
How long can products CE marked under the directives continue to be placed on the market and put into service? (Article 120.3)	From the date the regulation is fully applicable – May 26, 2020 – products may still be placed on the market or put into service as long as they still comply with the legacy directives and the notified body continues to be responsible for surveillance, and as long as their certificates remain valid up (see previous two rows).	In these cases, the MDR requirements apply in place of the directives' requirements for post-market surveillance, market surveillance, vigilance, and registration of economic operators and of devices.
How long can devices CE marked under the AIMDD or MDD that have been <u>placed on the market before May 26 2020</u> , before the new regulation applies, continue to be made available on the market? (Article 120.4)		Such devices can continue to be made available on the market or put into service until May 27, 2025 .
How long can devices CE marked under the AIMDD or MDD that are <u>placed on the market</u> , with a valid certificate, on or after May 2020, continue to be made available on the market or put into service? (Article 120.4)	A valid certificate is one that is issued before May 25, 2017, and is still within the validity period indicated on the certificate (unless the certificate was issued in accordance with Annex 4 of the directives, in which case it is void at the latest on May 27, 2022). Or, if the certificate is issued after May 25, 2017, its validity cannot exceed five years from date of issue, and will become void, at the latest, on May 27 2024.	Such devices can continue to be made available on the market or put into service until May 27, 2025 .
What happens to devices that did not have to comply with the medical device directives, but which have been allowed onto the market in the interest of health protection? Can these remain on the market after the regulations takes effect? (Article 120.9)	To be allowed on the market, these must have been granted authorizations by the competent authorities of the member states in which they are sold or used.	Yes, they will keep the validity indicated in the authorization
EUDAMED AND UDI		
UPDATED: How soon will manufacturers have to register their medical devices in the updated version of the Eudamed medical device database and notified body communicate updates relating to manufacturer certificates? (Article 120. 8)		The Regulation introduces a derogation in the registration requirements of the MDD which allows economic operators who already comply with the MDR rules on registration in the new Eudamed database to also be considered in compliance with the Directive registration rules. This is to encourage economic operators to use the updated Eudamed medical device database at the earliest possible opportunity, even when they are not otherwise in compliance yet with the IVDR.
What happens if there is a delay in setting up Eudamed? (Article 123, 3d)	If Eudamed is not fully functional on May 26 2020, then numerous requirements listed here and relating to where any information needs to be stored in Eudamed will apply six months from when the Commission has published a notice declaring that Eudamed has achieved full functionality.	While waiting for Eudamed to become fully functional, the corresponding provision in the MDD and AIMDD will continue to apply regarding exchange of information, particularly for vigilance reporting, clinical investigations, registration of devices and economic operators, and certificate notifications.
When do manufacturers need to register (or verify details) in Eudamed? (Article 123, 3e)	Registration also triggers the start of the process of keeping information updated	They need to register from 18 months after May 26, 2020, or six months after the date of publication that Eudamed is fully functional, whichever is the later.
When do notified bodies need to enter information regarding certificates issued, suspended, reinstated, withdrawn or refused, etc (Article 123, 3e)	This also applies to amendments and supplements to certificates and to restrictions imposed on certificates.	Notified bodies need to enter this information from 18 months after May 26, 2020, or six months after the date of publication that Eudamed is fully functional, whichever is the later.

UDI-SPECIFIC ISSUES		
What entities will assign Unique Device Identifiers? (Article 120.12)	GS1, HIBCC and ICCBBA will be considered the designated UDI assigning entities until the European Commission has officially designated UDI assigning entities.	AISBL had been removed from the latest version of the MDR.
From what point in time will GS1, HIBCC and ICCBBA be considered as designated UDI issuing entities? (Article 123,3i)		May 26, 2019
When will UDI carriers need to be placed on the label of devices and all higher levels of packaging? (Article 123,3f)	This depends on the risk level of the product. Deadlines for reusable devices are dealt with separately (see below).	May 26, 2021 for Implantable and Class III devices; May 26, 2023 for Class IIa and IIb devices; and May 26, 2025 for Class I devices.
How soon will the UDI carrier need to be placed on reusable devices? (Article 123,3g)	The UDI has to be placed on the device itself.	May 26, 2023 for reuse Implantable and Class III devices; May 26, 2025 for Class IIa and IIb devices; and May 26, 2027 for Class I devices.
SPECIAL-CASE DEVICES		
When can high-risk, innovative devices subject to the clinical evaluation consultation be assessed under that scheme? (Article 120.7)	Only once appointments have been made to the newly established Medical Device Coordination Group and the expert panels that will be involved in these consultations. Setting up this structure will be important to ensure that these products can be appropriately assessed in readiness for CE marking.	This applies to implantable class III devices and class IIb active devices intended to administer and/or remove a medicinal product.
What about devices manufactured using derivatives of tissues or cells of human or animal origin that are non-viable or are rendered non-viable? (Article 120. 10)	As long as a device has been legally placed on the market or put into service in accordance with the rules in force in the EU member states prior to the May 26 2020, the device may continue to be placed on the market and put into service in the member state concerned.	The MDR does not apply to devices which are manufactured using viable tissues or cells.
CLINICAL INVESTIGATIONS		
What about the validity of clinical investigations? (Article 120.11)	Clinical investigations that are underway in accordance with the MDD or AIMDD prior to May 26, 2020, may continue to be conducted.	As of May 26, 2020 , the reporting of serious adverse events and device deficiencies must be carried out in accordance with the new MDR.
When is it possible to apply for a coordinated assessment procedure for clinical investigations where the clinical investigation is being carried out in more than one EU member state? (Article 123,3h)	Up until May 27, 2027, the coordinated assessment procedure will be applied only to those member states in which the clinical investigation is to be applied and which have agreed to apply it.	After May 27, 2027 , all member states will be required to apply the relevant procedure
GOVERNANCE		
By when will member state competent authorities need to be listed by the EU and assume their role in implementation of the MDR? (Article 123,3b)		November 26, 2017
How soon will the paragraphs related to the setting up and roles of the Medical Devices Coordination Group apply? (Article 123, 3b)		November 26, 2017
How soon does cooperation between the member states and the European Commission need to be formalized by the Commission? (Article 123, 3c)		May 26, 2018

Wising Up On Intelligence Gathering To Win Medtech Tenders

OMAR AHMAD & CARLOS MECA

Tenders and large contracts are becoming the standard practice for procuring health care products in most European countries. For example, in the UK, the Department of Health, is currently preparing the roll-out of the Procurement Transformation Programme, a new procurement operating model that entails further consolidation of the procurement landscape and aggregating demand from the current 40% market share to above 80%. The focus of this program is on running competitive procurement processes and with transparent evaluation criteria.

Elsewhere, in Spain, smaller direct contracts are becoming a minority and tender consolidation is increasing. Following the steps of other regions, Madrid has recently awarded a single tender for the whole region. Other regions such as Castilla - Leon are expected to follow suit and rumors of national tenders are becoming louder. While in Germany, which has traditionally been a non-tender market, centralized contracts with the country's Top-10 group purchasing organizations can now secure majority of revenue for some product categories.

The situation is only getting more and more complex and challenging.

Although distinction between tender and contracting can be debated, the key consequences of both methods are identical: large procurement pooling, leading to increased business risks and a need to improve net price management. For the sake of this article, the term "tender" will represent both tenders in the classical sense of the word as well as contracting involving negotiations.

In order to make informed decisions and navigate safely along the rocky shores of the tender seas, developing robust tender intelligence capabilities is the key success factor. A structured database is the tool of choice to manage tender and contracting intelligence.



Shutterstock: Nikolay Litov

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TENDER INTELLIGENCE: KEY PILLAR OF TENDER MANAGEMENT

Robust tender intelligence can ensure that tenders are dealt with efficiently using centralized (be it at local, regional or global level) and easily accessible information. Best-in-class organizations systematically collect data such as bidding prices, volumes, evaluation criteria and scores, bidding competitors, and reasons for winning/losing. This information is then analyzed for general business monitoring as well to fine-tune future offers. However, a robust tender intelligence organization needs to address several challenges which can be grouped into four categories: information integrity, transparency of intelligence, process efficiency and success rate development. (See Figure 1.)

In order to make sure all aspects of successful tender management are covered,

a conceptual framework can be extremely helpful. For this framework, we can consider five key areas: organization, capabilities, governance, process and tools.

1) Adapting the tender management organization

There is no one-size-fits-all approach to tender intelligence; it needs to be tailored to the company's needs and organization.

The two key questions when it comes to setting up the organization is the geographical scope for tender intelligence and the level of centralization for intelligence management and responsibility. The latter is especially important as it will strongly impact internal buy-in and compliance.

Other areas to consider for the scope are the products/services to be included in a tender database as well as the nature of the deals to track (national/regional ten-

FIGURE 1

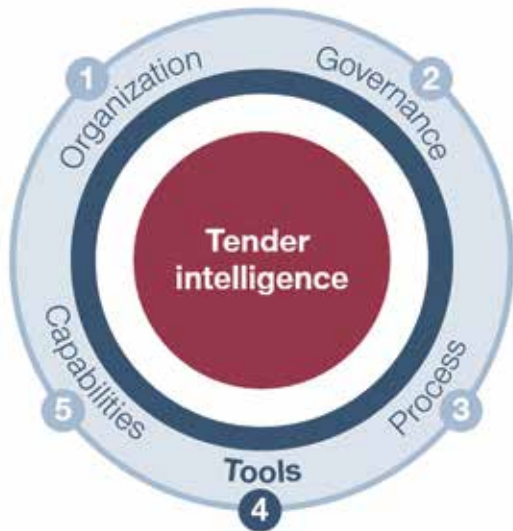
Most Common Challenges In Tender Intelligence Management



Source: Simon-Kucher & Partners

FIGURE 2

A Framework For Tender And Contracting Intelligence



Source: Simon-Kucher & Partners

ders only, large negotiated deals, smaller contracts, etc.). The database complexity goes hand in hand with the complexity of the tender market, along with the depth of the analysis required to be successful in that market.

2) Defining clear governance rules for information and decision management

A governance framework will essentially help answering the following three questions:

- Who owns the information?
- Who enters the information?
- Who has access to the information?

In our experience, a centralized tender

database owner with direct responsibility for the database ensures its integrity and makes sure it is used and maintained effectively.

In a highly decentralized organization, local markets may be in charge of managing local data and should have full rights for the database. Managing a large number of tenders will also work in favor of decentralized data entry. On the other hand, a limited number of tenders can be handled by a single owner who is then responsible for all data entry and who ensures its integrity. All aspects related to data ownership, data entry and data access should be clearly specified in a documented process.

3) Ensuring the right capabilities are available

Besides administrative resources (for managing data entry, milestone reminders, calendar entries, etc.), the effective use of a database requires analytical skills to extract meaningful insights from the collected information (regular reporting, ad hoc analysis, etc.). Analysis and administrative capabilities are part of the core business and, most of the time, should not be outsourced.

4) Defining an efficient and functioning process

An auditable process ensures that the tools and all of the resources are used optimally and should answer three basic questions:

- When is an action required? (eg when is a tender identified? When is a result available?)
- What is required? (eg data entry, extraction, analysis),
- Who is responsible? (eg tender analyst, tender manager)

Documenting and sharing this process will ensure that every relevant stakeholder understands his/her role and that the process is efficiently adapted as the organization grows in maturity.

5) Getting the right database tool to the right business

A robust tender and contracting database is the functional core of a tender intelligence initiative. Development of this tool should only start once the abovementioned areas have been at least outlined, if not fully determined. The tools should be designed around the (future) organization and not vice versa. We have identified three key design principles for developing the database tool: the software platform, the data entries and the functionalities.

Selecting the optimal software option

Depending on the maturity of the organization, the stability of the tender environment, the nature of the business (portfolio range, total number of tenders, etc.), and the tender goals, there are different options for implementing and running a tender database.

In its more advanced form, the database could be fully integrated into the CRM tool or the pricing system and communicate

of current contracts from the company and competitors and plotting market price development or win/loss statistics will be key to understanding the competitive positioning and improving decision-making.

A significant number of functionalities can be added to the database to improve the efficiency of tender and contracting management, including:

- Alerts on contracting milestones and calendars to plan the activities on a per tender basis
- Intuitive and automatically updated dashboards to monitor the tender status quo
- Import and export functionalities to be able to share key information or analyses and to update content without compromising database integrity
- Delivered volume to be able to

monitor customer compliance with contract terms

GETTING STARTED

When implementing tender and contracting intelligence capabilities, all of the key angles (organization, governance, capabilities, process and tools) should be aligned. This requires an iterative process where development options in one area are taken into account over the overall framework. Outlined in the flow char below is a proven approach in five main steps that require constant improvement monitoring.

In order to tackle such a complex issue, building a cross functional taskforce involving all key stakeholders is often the optimal approach. However, implementing such a solution will have implications across the organization (sales, marketing, market access,

pricing, legal, logistics, etc.) and will not be successful without clear leadership and top management drive and support.

For more and more markets and medtech sub-segments, success and failure will largely depend on how companies learn to navigate in a tender environment. It is now clearer than ever that access to information and the ability to use it efficiently will also be a critical competitive advantage that no healthcare company can neglect. A consistent and comprehensive approach to tender and contracting intelligence is not only a key success factor, but also a necessary condition for maintaining and growing a sustainable medtech business. ▶

Guest columns do not necessarily reflect the opinions of Medtech Insight.

Published online 05/11/17

COMPANIES

J&J Heading Into Fourth Pelvic Mesh Bellwether

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Opening statements are being heard this week in the Philadelphia Court of Common Pleas for a case brought by a Pennsylvania woman alleging she was injured by a pelvic mesh device made by **Johnson & Johnson's Ethicon Endo-Surgery Inc.** business unit. This is the fourth mesh-related bellwether case against Ethicon to be heard in the Philadelphia court.

Plaintiff Sharon Beltz initially filed suit against Ethicon in July 2013. Court records say she was implanted with Ethicon's *Gynecare Prolift* pelvic mesh in 2006 to treat pelvic floor prolapse, and needed revision surgery to remove the mesh in 2011. Beltz alleges she experienced complications including infection, incontinence and pelvic pain due to her treatment with the mesh.

The trial is launching fast on the heels of the third bellwether case. On April 28, a Philadelphia jury handed down a \$20m verdict against Ethicon that included \$175m in punitive damages. The plaintiff, Peggy Engleman, said the *TVT-Secur* mesh that was used to treat her stress



urinary incontinence was defective. It reportedly eroded within her body after just two months and required three surgeries to remove. But Ethicon argues that the risks should have been known to Engleman's doctors.

Engleman's attorney, Benjamin Anderson of Cleveland's Anderson Law Offices, told Delaware Law Weekly that he believed his client won the case because testimony from a former J&J consultant showed that an internal study had warned of the erosion risk.

Johnson & Johnson has maintained throughout the pelvic mesh trials that it isn't responsible for the patients' complications.

"We believe the evidence showed Ethicon's TVT-Secur device was properly designed, Ethicon acted appropriately and responsibly in the research, development and marketing of the product, and TVT-Secur was not the cause of the plaintiff's continuing medical problems. Therefore, we are disappointed with today's verdict and feel we have strong grounds for appeal," an Ethicon spokeswoman said in a statement.

Two earlier Philadelphia juries also sided with patients. In the initial bellwether trial in December 2015, the jury awarded \$5.5m in compensatory damages and a further \$7m in punitive damages. And in February 2016, a Philadelphia jury awarded \$3.5m in compensatory damages and \$10m in punitive damages to plaintiff Sharon Carlino. The decision has since been upheld in a state court. (*Also see "Judge Upholds \$14M Pelvic Mesh Award" - Medtech Insight, 10 Jan, 2017.*) ▶

Published online 05/11/17

Device Exec Pleads Guilty To Trade Secret Theft

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A former **Lutonix Inc.** employee has pleaded guilty to one count of theft of trade secrets in a Minnesota federal court, and now faces up to 30 months in prison and a fine of up to \$95,000

Christopher Barry was VP of research and development for the device-maker from 2007 until May 2015. In this role, he helped develop Lutonix's flagship drug-coated balloon project, the *Lutonix 035 DCB*, the US Department of Justice said in a press release. **Bard Medical**, which now markets the balloon, purchased Lutonix for \$225m in 2011.

According to DoJ, the theft occurred after Barry agreed to leave Lutonix to take on a role as CEO of startup firm Urotronic, which was founded by a former Lutonix employee. While preparing to change jobs, Barry allegedly took several computer files containing proprietary information from Lutonix for use at

Urotronic. He then uploaded the stolen files onto his Urotronic computer, and shared several of these documents with other Urotronic employees.

The stolen trade secrets cost Lutonix nearly \$534,000 in investigative and legal fees, Lutonix attorneys say in court filings.

"Urotronic's product was developed before Mr. Barry was hired and Mr. Barry had no involvement in the development of the Urotronic technology," Urotronic said in a statement. The company also says that it was unaware of the scheme and demanded Barry resign when the intellectual property theft came to light.

The US Federal Bureau of Investigation, the Criminal Investigation Division of the Internal Revenue Service, and the United States Postal Inspection Service helped investigate Barry's case. ▶

Published online 05/15/17

Senseonics, TypeZero Join Forces On Artificial Pancreas

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Under a non-exclusive agreement, Germantown, Maryland-based **Senseonics Holdings Inc.** will use its *Eversense* sensor, the first and only fluorescence-based implantable continuous glucose monitoring (CGM) sensor system, to integrate glucose readings into **TypeZero Technologies Inc.'s** *inControl* software platform. The software includes a series of algorithms for artificial pancreas solutions. Financial details of the agreement were not revealed.

Senseonics' Eversense sensor is unique in that it continuously measures glucose levels for up to 90 days, which eliminates the need for weekly sensor insertions. The sensor is inserted subcutaneously in the upper arm and wirelessly communicates with a smart transmitter, which is worn on the arm, to relay data to a mobile device with a diabetes app. The goal of the agreement is to integrate glucose readings from the Eversense sensor into TypeZero's artificial pancreas (AP) *inControl* software platform to automatically adjust and regulate insulin delivery via a user's insulin pump, the companies said May 12.

The integration will also allow TypeZero's decision support system to recommend optimal basal and bolus doses for insulin pen users, according to the firms.

"We're thrilled to partner with TypeZero with the goal of progressing the diabetes management field in providing solutions to help minimize the burden of diabetes for millions of people," said Tim Goodnow, president and CEO of Senseonics in a statement.

"We see the combination of our *inControl* technology with Senseonics' sensor as potentially a huge win for persons with diabetes," said Chad Rogers, CEO of TypeZero.

In this highly competitive race to bring an artificial pancreas to market, TypeZero has already teamed up with several other diabetes companies. (Also see "Advent Of Artificial Pancreas Tech To Galvanize Fast-Growing Diabetes Market" - *Medtech Insight*, 26 Apr, 2017.)

Just last month, the company announced it completed a worldwide license agreement to integrate and commercialize its technology into **Cellnovo Group's** mobile diabetes management system. CellNovo's Bluetooth-enabled micropump, which is in early development, is claimed to be the first patch-pump and mobile connected system. The companies expect their efforts will lead to a CE mark and product launch in 2018. (Also see "Cellnovo Targets 2018 Launch Of Insulin Micropump With Artificial Pancreas Tech" - *Medtech Insight*, 20 Apr, 2017.)

In addition, TypeZero licensed its technology to San Diego-based **Tandem Diabetes Care Inc.** to develop Tandem's next-generation *t:slim Insulin Pump*, a "smart" AP system that alerts patients with recommendations, including real-time advice regarding insulin basal rates, insulin bolus calculations and meals, and helps patients make better decisions regarding exercise. This product also holds promise for a market introduction next year.

Medical device giant **Medtronic PLC**, however, has long dominated the global insulin pump market. The company won US FDA approval last September for the *MiniMed 670G* insulin pump, which the firms describes as the world's first artificial pancreas device-based system (Also see "US FDA Approves First 'Artificial Pancreas' In Medtronic's MiniMed 670G" - *Medtech Insight*, 28 Sep, 2016.). The MiniMed 670G is expected to hit the US market this spring. ▶

Published online 05/12/17

BioTrinity 2017: Gut Potential, Drug Delivery Innovations And Partnering Opps

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Industry experts, investors and start-ups from across the pharma, biotech and medtech sectors gathered at the annual BioTrinity conference held in London this week (May 9-10) to explore partnering opportunities and future trends in the health care industry.

The two-day event opened with a discussion on the growing microbiome field which panelists explained held “huge potential” for life sciences companies. Tim Spector, CEO of **Map My Gut**, a consumer gut microbiome analysis service, said the technologies emerging from this field could be “bigger than genetics,” and “more useful than DNA” when looking at health outcomes but big pharma were yet to realize its possibilities.

Denise Kelly, an investment advisor for Paris-based venture capital firm **Seventure** echoed Spector, saying the field is growing rapidly, particularly in France, which has become a major “hub of excellence.” Seventure currently manages the Health for Life Capital fund which focuses primarily on microbiome-based tech innovations in Europe, North America and Asia. “In the period I’ve been with Seventure I’ve seen how the field is growing exponentially,” Kelly told *Medtech Insight*. “There are new start-ups emerging regularly and the ones that currently exist are doing extremely well.”

Kelly said the Health For Life Capital Fund has raised in excess of €160m and is keen to expand its microbiome portfolio. “Before making investments we look at the credibility of the science, the team, the academics and the work they’ve got. It has to really hold together,” she said. “Sometimes we find that companies are coming to us far too early and their pre-clinical data is just not strong enough – that’s a risk we aren’t willing to take so it’s really looking at a package that has done as much as it can in preclinical phase to

really show efficacy. We also like to see they have a pipeline of opportunities and are not just one-product companies.”

Kelly highlighted **Enterome** and **Vedanta** as two key companies in Seventure’s portfolio that have massive promise. French company Enterome has developed two metagenomics platforms, one that characterizes the metagenome linked to a particular disease phenotype and another that screens genomic and metagenomics libraries to discover novel drugs and targets. The company has already inked partnerships with major businesses including **AbbVie**, **Bristol-Myers Squibb** and **Takeda**.

“There is a clear evidence that you have dysbiosis in disease and what we’re seeing now is incredible sequencing ability but also incredible computational ability to really do a deep dive and look at bacteria at strain level,” said Kelly. “If you use a particular technology you can look at the bacteria on a genus level but if you use metagenomics, you can look right down to strain level. You can have a single species where you have multiple strains and the function is very distinct so really you’re looking at high level resolution and high quality but basically being able to identify the bugs involved in causality driving disease, so the technology is moving that way.

“Enterome is one of the first companies to finish Phase I on their lead product, EB8018, a molecule that blocks attachment of the pathogenic stream involved in the pathology of Crohn’s disease,” said Kelly.

Kelly added French biotech **Eligo Biosciences** was an exciting company on the rise. The start-up raised €2m in a Series A round led by Seventure for its platform gene-editing technology that delivers CRISPR via phages to target bacterial strains. She explained the immune-oncology field was also catching on to the potential of the microbiome field, as research shows certain immunotherapies

are reliant on the gut’s microflora. “Enterome are now working in this area with BMS and looking at how microbiota influences the efficacy of immune modulators such as checkpoint inhibitors which are big in immunotherapeutics,” she said.

But despite the hype, Kelly said the field still faced a series of challenges. “The main challenges with this type of technology are that it’s not straightforward to make a live bacteria therapeutic. You have all the challenges of manufacturing, safety and the regulatory framework. But there’s companies now leading the way and starting to produce products that are being tested in human so in all, it’s an extremely exciting time.”

DRUG DELIVERY DIFFERENTIATION

Drug delivery innovations have always been a strong theme among the companies attending BioTrinity, with the event presenting fertile ground for partnerships between drug delivery specialists and pharma firms.

One of the companies presenting at BioTrinity’s medtech showcase was **Medherant Ltd**, a University of Warwick spin-out that has developed the *TEPI Patch*, a transdermal drug delivery platform. Speaking to *Medtech Insight*, CEO Nigel Davis said that the young company, founded only two years ago, is planning a Series A financing round at the end of this year. It is aiming to raise up to £10m (\$12m) in this round to fund pivotal clinical studies of the first couple of TEPI Patch products for pain relief, notably a patch for delivering ibuprofen (Medherant’s lead product) and another for lidocaine.

What differentiates the TEPI Patch from other currently available drug delivery skin patches is its adhesive, which Medherant had originally licensed from Bostik, the multinational adhesive and sealant technologies specialist. The adhesive has been

designed to be compatible for high drug loadings, while offering steady delivery of drug and good adhesion over a prolonged period. "Because we can achieve a higher loading of drugs, this means we can make a smaller patch that delivers the same dose of drugs than other patches," explained Davis. "Other patches are big, not very comfortable and some don't stick very well. But the TEPI Patch sticks well, is very comfortable to wear and does not leave any residue on the skin."

Additionally, the TEPI Patch has shown to have very low levels of residual drug at the end of the delivery period, continued Davis. "There is very little drug left on the patch; so, if it is a hormone that the patch is delivering, there will be less of an environmental impact after the patch is disposed. And if it is a controlled drug, there would be less potential for drug abuse."

While ibuprofen is widely available in pill form and as a topical gel or cream, there is an absence of ibuprofen-delivery patches on the market. "There are patches that provide pain relief but these are heat patches, and do not deliver any drugs," said Davis. Medherant's ibuprofen TEPI Patch will be designed as a 24-hour patch, to be sold directly to consumers. The firm does not intend to do the commercialization itself, but to license it to a larger pharmaceutical partner to sell.

Davis told *Medtech Insight* that there are two strands to Medherant's business model: the first, is to develop TEPI Patches for well-established drugs, like it is doing with ibuprofen and lidocaine. "We know of at least 30 different drugs that can be used with our patch," he said. The second strand of the company's business model is to partner with pharma companies that are clinically investigating a new molecule that could be delivered using the TEPI Patch.

To date, Medherant has received around £2.2m in seed funding from UK investment group Mercia Holdings, business angels and a number of high net worth individuals. This will help the company build out its management team as it preps for its Series A fundraising and safety and efficacy studies which are expected to start at the end of 2017. Davis estimated that it will take a year for the clinical studies to complete,

before submitting its regulatory approval application for the ibuprofen patch at the end of 2018.

Medtech Insight also met up with another company at BioTrinity who has also developed a novel drug delivery approach – very different from Medherant's in terms of the delivery technique and the type of drug – and has just embarked on the clinical trial path.

French biotech firm **Eyevensys** is targeting the ophthalmic disease sector with its *EyeCET* platform technology, from which the lead product, *EYS606* for non-infectious uveitis (NIU), has been used to treat the first patient of a Phase I/II trial.

EyeCET comprises two components. The first are the plasmids, non-viral nucleic acid-based drugs which, when inserted into a cell, act like "a computer program" for the cell to express particular therapeutic proteins; *EYS606* uses a plasmid encoding for the production of an anti-TNF α therapeutic protein (TNF α is a cytokine that has been shown to play a pivotal role in mediating intraocular inflammation in NIU patients). Eyevensys uses plasmids licenced from US biopharma company, Nature Technology Corporation (NTC). "These particular plasmids have already been used in clinical studies in oncology but we have an exclusive licence from NTC to use their plasmids in the ophthalmic field," said Eyevensys CEO Raffy Kazandjian.

The second, and what Kazandjian believes to be the critical, component of the *EyeCET* platform is the company's proprietary electro-transfection injection device for delivering the plasmids into the cells of the eye's ciliary muscle. The device is designed to facilitate the placement of the electrodes in the ciliary muscle of the eye; once the electrodes are in position, the plasmid drug is injected into the ciliary muscle and short electrical pulses are delivered to create temporary pores in the cell membranes, allowing the plasmid drug to enter the cells.

The electro-transfection procedure using Eyevensys' device takes less than five minutes. Kazandjian told *Medtech Insight* that the *EyeCET* offers not only a less invasive approach than the intravitreal injections currently used for delivering anti-VEGF

medications for back-of-the-eye macular disease, but also a more cost-efficient solution as the ciliary muscle would express the therapeutic protein over a prolonged period, obviating the need for monthly injections. Kazandjian said that up to six months of protein expression have been observed in animal models following treatment with *EYS606*. "We are hoping to replicate the results we have achieved with *EYS606* in animal models, treating NIU patients once- or twice-yearly."

The Phase I/II trial for *EYS606* aims to demonstrate the safety and tolerability of treatment. It will recruit initially nine patients with severe NIU from France and the UK, and extend this to 15 patients with slightly less severe NIU, to confirm safety and detect early clinical signs of efficacy, said Kazandjian.

Eyevensys has to date raised €10m in equity financing and received around €2.5m in non-dilutive funds. It has a further €1.3m in committed venture capital which will help support the Phase I/II study. Early results from this trial are expected around the end of this year and by the second half of 2018, the plans are to start a Phase II study in the EU and US to establish clinical feasibility, safety and efficacy of *EYS606* in NIU patients and demonstrate sustained release of the therapeutic drug.

Pending positive Phase II data, the company hopes to file for conditional approval of *EYS606* at the end of 2020.

Kazandjian said Eyevensys has successfully expressed around 20 proteins with the *EyeCET* technology and some of these can target eye diseases with large unmet needs. Hence, the company is building a portfolio of products addressing major eye diseases and may potentially partner with other companies to develop solutions in other major ophthalmic indications. ▶

Published online 05/10/17



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To get a list of early-stage medtech companies that were showcasing their technologies at BioTrinity 2017, access the full article at <http://bit.ly/2q67oxZ>

HRS 2017: Medtronic And Boston Scientific's Less-Invasive CRM Devices Perform As Hoped In Real-World Registries

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New post-market registry data shows that the first two FDA-approved cardiac rhythm management devices without transvenous leads are performing about as well as could be hoped in the “real world.”

At the Heart Rhythm Society Scientific Sessions in Chicago on May 11, Mikhael El-Chami of Emory University in Atlanta reported acute results from 795 patients in the post-approval registry of **Medtronic PLC's Micra** transcatheter single-chamber pacing system and Michael Gold of the Medical University of South Carolina in Charleston presented the acute results from 1,637 patients in the post-market approval study of **Boston Scientific Corp's S-ICD** subcutaneous implantable cardioverter defibrillator.

MICRA MATCHES, IMPROVES UPON PRE-CLINICAL PERFORMANCE

The US FDA approved Micra in 2016 based on six-month data from a 725-patient investigational trial. As a condition of approval, Medtronic agreed to conduct a post-approval study with at least 1,830 “real-world” patients and, in January, CMS issued a coverage with evidence development policy on leadless pacemakers, confining Medicare coverage of leadless pacemakers to FDA-approved clinical trials. (Also see “Leadless Pacers Would Only Be Covered In Clinical Trials Under Medicare Proposal” - *Medtech Insight*, 16 Nov, 2016.)

“In an investigational trial, there are always questions that remain unanswered, because in an investigational trial, you highly select the operators – they have a certain level of skill and are experienced. You also restrict access to some patients. You don't take every patient,” El-Chami told *Medtech Insight*. “So you always wonder if the data obtain in the investigational trial will translate you open access to this technology. That's why the

post-approval registry is important, because it plans to assess how the device will perform in the real-world and in the hands of less experienced operators.”

In the data presented by El-Chami, Micra was successfully implanted in 792 of 795 patients (99.6%) by 159 different implanters at 97 centers in 20 countries. 86.6% of the physicians implanting Micra in the registry were doing so for the first time. The average pacing capture threshold at implant/pre-hospital discharge was 0.66 volts. The use conditions of subjects with at least 180 days of data suggest that the median battery longevity for Micra will be about 15 years.

Through 30-days post-implant, there were 13 major complications in 12 patients – including cardiac effusion/perforation, device dislodgement, and sepsis – for a major complication rate of 1.51%. By comparison, in the pre-market investigational trial, the device was successfully implanted in 719 of 725 patients (99.2%) and the major complication rate was 2.89%. El-Chami emphasized that the rates of pericardial effusion, device dislodgement, and infection were very low and confirm the positive results of the pre-market investigational trial.

Medtronic expects its leadless pacemakers will produce fewer complications over the long-term – especially infections – than standard pacemakers that required a transvenous lead. So this patient cohort will be followed for up to nine years to determine the long-term benefits of leadless pacemakers, “which is one of the longest follow-ups for any kind of device,” El-Chami said.

“When you look at the Micra investigational study, the results were so good in terms of absence of infection, absence of dislodgement, success rate. The only question mark that could have been placed on the investigational trial was the rate of pericardial effusion [which

was 1.6%],” he said. But the pericardial effusion rate was only 0.13% in the post-approval registry.

While the acute data are very encouraging, the longer term data will show if Micra can match the overall performance of traditional transvenous pacemakers and if the leadless concept can be applied to more complex devices, such as a leadless dual-chamber pacemaker, El-Chami said. (Also see “St Jude Sets Sights On Year-End US Approval For NanoStim” - *Medtech Insight*, 7 Sep, 2015.)

“How could you improve on a 99.6% implant-success rate? In medical technologies or surgery, you will never see a zero percent complication rate. That's unheard of. So it's very hard to improve on this particular device,” he said. “What I'm looking for in the future is if there will be dual-chamber [leadless] systems. These are the big next steps, in addition to having the long-term follow-up on these single-chamber pacers.”

REAL WORLD S-ICD PATIENTS ARE SICKER THAN THOSE IN PREVIOUS STUDIES

Boston Scientific's S-ICD, a technology originally developed by Cameron Health, is implanted just under the skin and detects arrhythmias with a subcutaneous lead rather than an intracardiac lead, so it is not as susceptible to lead failure, thrombosis, or infection. FDA approved S-ICD in September 2013 based on data from a 330-patient single-arm study, and then S-ICD also matched the performance of conventional ICDs in the EFFORTLESS registry. (Also see “Subcutaneous ICD Matches Conventional Defibrillators In Registry” - *Medtech Insight*, 3 Apr, 2014.) The agency approved the MRI-compatible version of S-ICD, *Emblem MRI S-ICD* in 2016. (Also see “MRI Labeling For Boston Scientific's Emblem MRI S-ICD Approved By US FDA” - *Medtech Insight*, 10 Aug, 2016.)

Boston Scientific Emblem MRI S-ICD



Photo credit: Boston Scientific

As a condition of the 2012 approval, the FDA required a post-approval study with about 1,600 patients from at least 50 different US centers, to be followed at least five years. At the HRS conference, Gold presented 30-day results from 1,637 patients treated at 86 US centers.

He explained that the early clinical trials of S-ICD were enriched with younger patients with less left ventricular systolic dysfunction and fewer comorbidities than typical transvenous ICD population, which makes comparisons between the S-ICD and transvenous systems difficult. So the post-market registry was designed to not only show the S-ICD's performance in the real world but collect information on which patients are choosing to get an S-ICD rather than a traditional ICD with a transvenous lead.

The patients in the post-approval registry were more like "typical" ICD patients than the populations studied in previous S-ICD studies and had high rates of comorbidities, Gold said. But despite a sicker patient cohort, the acute success rate with S-ICD in the study was high, as were the rates of acute conversion of induced VT/VF episodes and freedom from perioperative complications. "These data suggest that inclusion of patients with broader comorbidities across more implanting centers will not adversely impact short term complication rates," he said.

"The implantation success-rate [with S-ICD] is high and short term complication rates are acceptable," Gold said. The 30-day complication-free rate was 96.2%. The 30-day infection rate was 1.2%. Predictors of complications included younger age, higher body-mass

index, and diabetes. Testing of the device showed conversion of induced VT/VF was successful in 98.7% of patients, with first-shock conversion achieved in 95.6%.

In the study, 91.2% of patients could have also received a traditional ICD and that simple patient preference was the reason 52.4% of the patients got the S-ICD. Age, activity level, and infection risk were among the other reasons why the patient and their physician believed the S-ICD was a better choice. Only 8.8% of the patients in the study got an S-ICD because it was the only viable choice. These patients had either adverse anatomy preventing the implantation of a traditional ICD with a transvenous lead or a high risk of infection.

About 78% of the patients in the registry were getting an S-ICD for primary prevention of sudden cardiac death, compared to 63% in the EFFORTLESS study, and 74% were suffering heart failure, compared to just 29% of the patients in EFFORTLESS. In the post-approval study, 62% of the patients had hypertension, compared to 24% in EFFORTLESS; 34% were diabetic, compared to 12% in EFFORTLESS; 26% had kidney disease, compared to just 9% in EFFORTLESS.

ECG screening was successful in at least one, two, or three vectors in 100%, 93.8%, and 51.4% of patients, respectively, but multivariate analysis found no clinical predictors of the number of vectors passed. The implanting physician used a two-incision technique in 52.2% of cases in the registry and the patients were under general anesthesia 64.1% of cases. The device had to be repositioned during the initial procedure in 2.8% cas-

es and had to be repositioned during the next 30 days in 0.7% of cases.

All of the patients in the S-ICD post-approval study will be followed for at least five years. Boston Scientific is also sponsoring the 1,800-patient MADIT S-ICD trial, comparing Emblem MRI S-ICD to conventional medical therapy in patients with a prior myocardial infarction, diabetes, and a relatively preserved ejection fraction of 36-50%.

BOSTON SCIENTIFIC UPDATES EMPOWER PROGRESS

Boston Scientific is also developing the *Empower* modular cardiac rhythm management system which will include a leadless pacemaker to complement Emblem. During Boston Scientific's May 11 investors conference, Joseph Fitzgerald, the president of Boston Scientific's Rhythm Management business, said the leadless pacemaker is still in the "development phase," but the company is already planning a basic approval study for the leadless pacemaker alone and a trial of the S-ICD in combination with the leadless pacemaker for patients who need an ICD and anti-tachycardia pacing.

At HRS, Fleur V.Y. Tjon of the Academic Medical Center in Amsterdam, and colleagues, presented data from animal trials demonstrating that this combined modular therapy system can deliver appropriate chronic functionality, communication, and anti-tachycardia pacing. Also, Ryan Cunnane and colleagues at the University of Michigan presented the case of a 74-year-old man with atrioventricular block, ventricular tachycardia/ventricular fibrillation arrest, and persistent atrial fibrillation; Cunnane's group successfully treated this patient with both a Micra pacemaker and an Emblem S-ICD. "To the best of our knowledge this case represents the first in-human simultaneous implantation of a leadless pacing system and a subcutaneous ICD," Cunnane et al. concluded. "We demonstrated that the systems are safe to use together and represent an exciting new treatment option for patients." ▶

Published online 05/14/17



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