MedTech Strategist

MARKET PATHWAYS

Global Medical Device Regulatory, Reimbursement & Policy Review

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EU MDR: Welcome to the New Reality

Managing Change in Global Medtech Regulation

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WE GET IT.

The global medical device industry is evolving rapidly, and more change is coming. Making sense of it all, deciding what is relevant and what isn't, is getting increasingly difficult.

Written by the industry's most experienced and well-connected subject matter experts, our flagship publication, MedTech Strategist was created to provide your company with leverage and a business advantage that adds to your expertise and enriches the value of your company's portfolio, becoming an indispensable resource for you and your entire organization.

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Pointing The Way: *MedTech Strategist Market Pathways*

A message to medical device makers: your pick of market pathways is growing in volume and complexity. Some are newly placed express lanes. Others are freshly fitted with speed bumps. And some pathways face the prospect of major bumper-to-bumper traffic. But getting from Point A to Point B in medtech is not what it used to be—there are more decisions, more demands, and more data.

The context: as technology rapidly advances and the medtech industry expands its global reach, policymakers are coming up with new routes and checkpoints for incorporating medical devices and diagnostics into patient care, healthcare systems, and national economies.

In some cases, governments are trying to address barriers to innovation. For instance, the Breakthrough Device Program in the US, the Innovative Device Pathway in China and the UK's Accelerated Access Collaborative are designed to support enhanced regulatory and payor collaborations and accelerated paths to market for especially promising technologies. But new programs like these, while offering advantages, present a new range of questions for companies about market strategy that can add complexity: Will my product qualify? What's the application process? Is it worth pursuing?

On the flip side, concerns about ensuring patient safety and protecting national budgets lead some decision-makers to add market barriers. The current process in Europe is the prime example. New regulations, forged in response to safety concerns, and a backlogged implementation process are causing an existential crisis for some in the EU medtech market.

Meanwhile, the high price tag of new device innovations, including technologies like robotic surgery, is giving governments, insurers, and hospitals some pause. In this context, new value-based routes to adoption are forming, putting more emphasis on things like cost effectiveness and risk sharing. And regions that might have been considered more of an off-roading experience in the past are moving into the regulated arena. An array of countries in Asia and Latin America, for instance, that haven't previously had any or have very minimal device-specific regulations are formalizing more rules of the road.

In short, making sense of the full landscape of risks and opportunities in medtech has never been more complicated. And that is why we've launched *MedTech Strategist Market Pathways*. To help point the way. In this inaugural issue and in all of our efforts ahead, our goal is to leverage this team's decades of experience in covering the device and diagnostics industries to explore the barriers, spotlight opportunities, talk to the decision-makers and, importantly, tell the stories of companies that are persevering on different points along the myriad medtech market pathways. We will also keep you in the loop on all the incremental changes in regulations and policies each week that shape these pathways over time.

So, let's get to it.

First, the barriers: some key opinion leaders on the EU medtech market and regulations discussed some of the dirty details of the oncoming Medical Device Regulation at *MedTech Strategist*'s recent *Innovation Summit* in Dublin. We captured their pretty depressing conversation here **(p. 38)**. And we also provide a catch up on the bits of MDR progress that have been made in recent months **(p. 9)**.

The company stories: Tracy Schaaf delves into the experiences of IDx, a firm on the frontier of regulatory and reimbursement policies facing artificial intelligence technology **(p. 26)**.

The decision-makers: Jeffrey Shuren is coming up on 10 years as head of the FDA's device center—he is itching to move faster experimenting with innovative new regulatory strategies, he tells us **(p. 20)**.

The opportunities: It's not always been easy for new technology to find a place in Medicare, but some promising signals are coming out of the Centers for Medicare and Medicaid Services **(p. 32)**.

Also inside: expert tips, data, and news updates.

I am so excited to be launching *Market Pathways* along with the experts at *MedTech Strategist*. I look forward to hearing feedback from you, the medtech community, about this publication, and about your experiences in the realm of regulation, reimbursement, and market access. Please email me (at the address above) with any comments you have about this inaugural issue or suggestions about things you would like us to cover in upcoming issues. We want to address the topics of most concern to you.

For now, happy traveling—on whatever pathway you find yourself.

MedTech Strategist
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June 2019 Cover

US Capitol Building, Washington DC

Political partisanship is at an all time high, but the device sector is looking to US lawmakers to reform diagnostic regulations, repeal the device tax, and increase FDA's budget this session.

THIS ISSUE

Sections

Features

THE NEWS THIS MONTH

>>REGULATORY

One more notified body.

TÜV SÜD became the second notified body to be designated under the oncoming EU Medical Device Regulation May 23. That is a far cry from the almost 60 organizations currently designated under the EU device framework, but it's progress. With the regulation taking effect in May 2020, many in industry are wondering about the feasibility of staying on the market. (*See EU Regulations Catch-Up and EU MDR: Welcome to the New Reality, this issue.*)

Australia annual reports.

The Australia Therapeutic Goods Administration says it will no longer be sending around reminders to companies to submit annual reports. Annual reports are due for Class IIb implantable devices, Class III devices and Class IV IVDs every Oct. 1, for the first three years after a device is approved, TGA reminds companies. (*See "Aussie Regulatory Reforms Under Way," this issue.*)

India device scope expands.

India's Central Drugs Standard Control Organization (CDSCO) captured a dozen more devices in its new device regulatory scheme May 15. The country established medical device-specific regulations for the first time in 2017 and has since been "notifying" newly regulated devices into risk categories. Imaging equipment, including CT, MTI, PET and X-ray, have been newly designated as moderate-to-high risk (Class C), as have external defibrillators and glucometers. Meanwhile, digital thermometers and bone marrow cell separators are among those now in the comparatively lower-risk Class B category. Hundreds of other devices have already been risk-classified, which helps determine each product's marketing requirements in India. Another factor is whether a device has been approved by other global regulators.

Standards shortfalls.

The European Commission failed to include several device standards that will be central to supporting company compliance to the new regulations, among other lapses, in its recent request to standards organizations, MedTech Europe said May 28. The trade association is calling on stakeholders to pressure the commission to take more action.

Pre-cert test.

FDA is looking for volunteers to help test its proposed precertification program for digital health software as a strategy to streamline product reviews when the agency gains trust in a firm's processes. Companies developing software as a medical device for a 2019 De Novo or 510(k) submission can email FDAPre-CertPilot@fda.hhs.gov if they are willing to undergo an "excellence appraisal." But FDA will not be granting any precertifications this year, and no specific incentives for companies are mentioned.

Staple scrutiny.

An FDA advisory panel signaled support May 30 for FDA's proposal to "up-classify" surgical stapler devices from Class I to II so they will require 510(k) clearance to enter the market. The meeting was the latest step in FDA's stepped-up scrutiny of staplers and implantable staples in response to a large number of adverse event reports filed for the devices in recent years. (About 110,000 from 2011 to 2018, according to FDA's updated report at the panel meeting.) The agency also recently issued new labeling recommendations in a draft guidance document and it designated a recent product withdrawal action by Johnson & Johnson/Ethicon Endo-Surgery for Intraluminal Staplers as a Class I recall on May 16.

>>DATES TO REMEMBER

June 19-20: FDA's Circulatory System Devices Panel will meet to provide input on mortality risk in peripheral arterial disease patients treated with paclitaxel-coated balloons and -eluting stents.

June 20: The next (closed-door) meeting of EU's Medical Device Coordination Group, the primary body assisting the European Commission to implement the new Medical Device Regulations.

June 24: Final transcatheter aortic valve replacement national coverage determination due from the Centers for Medicare & Medicaid Services on a proposal that would reduce the procedural volumes required for hospitals to establish new TAVR programs.

>>REIMBURSEMENT AND TECH ASSESSMENT

Medicare reconsiders next-gen sequencing.

In 2018, the Centers for Medicare & Medicaid Services granted national coverage to next-generation sequencing (NGS) for patients with late-stage cancer to help inform drug selection. But CMS later clarified that the policy did not cover NGS to identify hereditary (or germline) cancer syndromes in early-stage cancer patients. The agency is now reconsidering that second part in response to public pushback from physician, patient and laboratory groups. CMS opened a national coverage analysis for germline NGS April 29 – a proposed decision is due in October.

EU digital health focus.

More targeted criteria, funding and evidence-generation guidelines are needed to support reimbursement of digital products in Europe, industry groups argue. The European Commission's eHealth Stakeholder Group, led by EU device trade association MedTech Europe, made the case for a more robust European-wide and country-by-country focus on developing bespoke processes for reimbursing evolving digital tools in a "guiding principles" document posted in May.

Germany pursues digital health reimbursement reforms.

The German Health Ministry circulated draft legislation May 15 to improve reimbursement and patient access to digital health technologies in its country. Among its provisions, the bill would establish a fast route to reimbursement for "low risk" digital health applications or devices that recognize, monitor, treat or alleviate disease. The Federal Institute for Drugs and Medical Devices would select digital applications that qualify for the reimbursement. Products that don't yet have evidence supporting positive healthcare benefits can qualify for up to 12 months, or more, of provisional coverage while the company collects evidence in support of the technology.

NICE notes.

The UK National Institute for Health and Care Excellence found two device procedures to be lacking in sufficient evidence to support non-research use in draft consultation guidelines issued in May: high-intensity focused ultrasound for glaucoma and implant insertion for "prominent ears." Comments on the proposals are due June 20.

>>APPOINTMENTS

New MDMA chair.

McCAULLEY

DJO President Jeff McCaulley is the new board chairman of the Washington, DC-based trade association Medical Device Manufacturers Association. He was elected to the post during MDMA's annual meeting in May, replacing Paul LaViolette, executive chairman at SV Health Investors. McCaulley says repeal of the medical device tax, a speedier reimbursement process and successfully reauthorizing user fees are his top policy priorities.

AdvaMed state official.

BHATT

Manthan Bhatt has joined AdvaMed as director of state government and regional affairs, the trade group announced May 3. Bhatt will help shape the group's medtech advocacy efforts at US state capitols. He moved from a similar role at the American Academy of Orthopaedic Surgeons.

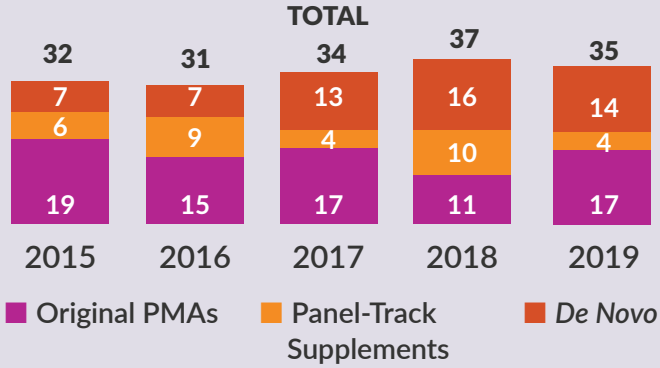
MAY MARKET PATHWAYS SCORECARD

A snapshot of stats and facts for the medtech regulatory and policy community.

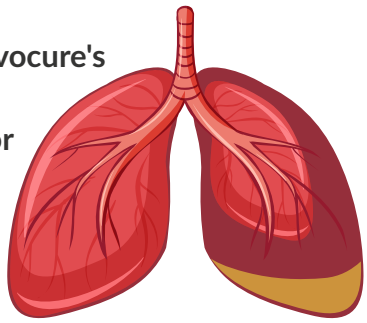
FDA APPROVALS

8 novel devices in May

Novel Device Approvals: Year-To Date



FDA also approved Novocure's humanitarian device exemption for its Tumor Treating Fields device (NovoTTF-100L) for malignant pleural mesothelioma, based on an 80-patient single-arm trial.



RECALLS

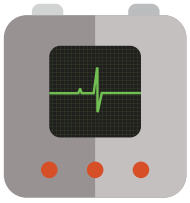
23 CLASS I

381 CLASS II

12 CLASS III

WARNING LETTERS

3 DEVICE WARNING LETTERS ISSUED BY FDA



Two makers of batteries for automated external defibrillators were cited for quality system and other compliance issues in May 9 warning letters.

GUIDANCE

FDA's device center finalized 6 guidance documents in May, on imaging device standards, lasers, organ preservation devices and pre-submissions meetings.

GLOBAL UPDATE

$24,345

New Health Canada application fee (in Canadian dollars) for Class IV medical devices.

2

Notified bodies that have now been designated under the EU Medical Device Regulation.

1,254

Device types currently exempted from clinical trials by China's National Medical Products Administration.

Sources: US FDA; Health Canada; China NMPA

STORIES WE'RE TRACKING

EU Regulations Catch-Up:

Where Things Stand One Year from Lift Off

Europe's new Medical Device Regulation is scheduled to activate next May, but the necessary frameworks are far from ready. Still, progress has picked up a bit in recent months. Here's a quick look at recent steps forward and remaining barriers.

>>David Filmore

Some late-May progress in the designation of notified bodies under the looming European Medical Device Regulation (MDR) added a touch of brightness to an overall bleak picture for device companies.

The bleakness was on display at *MedTech Strategist*'s recent Innovation Summit in Dublin, where speakers lamented the prospects for a European slowdown in new device launches, and even the chance of current products patients rely on to drop from the market under the MDR. (*See EU MDR: Welcome to the New Reality," this issue*). The fundamentals of the new regulation have raised concern—for instance, new requirements for submitting comprehensive bench and pre-clinical data will make it difficult to for a company to rely on comparisons to another firm's marketed products to support the launch of iterative device innovations.

But the current urgency is focused on major, and realistic, fears that the new EU regulatory framework, which relies on accredited notified bodies to oversee device companies seeking market entry, will not be ready in time for its May 2020 go-live date. One of the central issues is the fear that there will not be enough

notified bodies designated under the MDR in time, particularly considering that all current devices need to be re-validated to remain on market, in addition to new devices entering the market. MedTech Europe CEO Serge Bernasconi made this case at the Dublin meeting and distilled the point in a subsequent open letter to the European Commission.

"This situation is clearly untenable, and time has run out to build a functioning regulatory system," Bernasconi wrote in an April 15 letter. "This set of circumstances will profoundly disrupt the medical technology internal market and create yet another significant 'Cliff Edge' putting patient safety, healthcare services and EU healthcare environment in a major disarray."

Despite the warnings, the commission has publicly expressed calm and confidence about implementation. And, it does appear that some tangible progress has picked up in recent months.

Meanwhile, word is circulating that individual EU countries are working together to figure out a "plan B" if the system is not ready to accommodate the full load of devices by next May, or even by 2024, when the transition period for select devices that are able to rely on prior certification under the current Medical Device Directives runs out. The goal is to find a way to rely on national laws to allow products to remain on the market if the MDR structures and/or enough notified bodies are not in place, perhaps by relying on country-by-country certifications, rather than an EU-wide CE mark.

On May 29, MedTech Europe joined six other European trade groups, including the dental industry, hearing aid industry and healthcare distributors, to implore the commission to work with member states to accelerate implementation.

Here is a look at key steps recently taken and crucial issues that remain unresolved:

The notified body void: The European Commission unveiled the second notified body to be accredited to evaluate companies under the MDR on May 23. German-headquartered TÜV SÜD joined BSI Assurance UK as the only two notified bodies with that distinction. As of mid-May, the commission said 39 notified bodies have applied for designation under the MDR (and an additional 10 have applied for designation under the *In Vitro* Diagnostics Regulation [IVDR], which takes effect in 2022). A European Commission official speaking in Paris at MedTech Europe's annual meeting in May cited hopes of getting close to 20 notified body designations by the end of 2019.

While that would be significant progress, it would still be a far cry from the approximately 80 notified bodies that were designated under the current device and IVD directives until recently, and even the 58 notified bodies that remain active under the directives in the face of enhanced oversight.

Eudamed, UDI progress: One core reform in the new regulations is the mandate to establish a new European Database of Medical Devices (Eudamed) to provide more transparency about what devices have received CE marks and to track safety and other device information, with the help of a unique device identifier (UDI) system. There are still questions about whether Eudamed will be ready in May 2020 when the MDR goes into force. But EU Medical Devices Coordination Group (MDCG) issued guidance in mid-April that provides some cushion to help ensure device manufacturers will be able to comply with Eudamed requirements.

The MDCG guidance clarifies that manufacturers will have 18 months after the MDR application date, or 24 months if implementation of Eudamed is delayed, to register devices in the database. A second guidance explains how devices that remain on the market under the legacy device directives for an allowed transition period after the new regulations take effect can be registered into Eudamed under the same timeline.

WORD IS CIRCULATING THAT INDIVIDUAL EU COUNTRIES ARE WORKING TOGETHER TO FIGURE OUT A "PLAN B" IF THE SYSTEM IS NOT READY TO ACCOMMODATE THE FULL LOAD OF DEVICES BY NEXT MAY.

Such legacy devices would be assigned a temporary device ID to be registered in database. Once they are certified under the new regulations, a formal UDI would be assigned.

In May, the commission issued several additional guidelines and documents on technical elements for the European UDI and Eudamed data exchange. Implementing acts, which are necessary for each EU member state to adopt EU-wide regulations, are currently in the works for both UDI and Eudamed.

When can extra scrutiny be skipped? Modifying a currently marketed high-risk device to comply with the European Union's new Medical Device Regulation (which take full effect in May 2020) will not be enough to subject the device to the possibility of extra clinical data scrutiny by European Commission-appointed expert panels, a guidance from late March clarified. The centralized scrutiny procedure is one hot-button area of reform in the EU MDR, where, for the first time in Europe, review of clinical data for certain class III and IIb devices could go beyond the notified body that a company contracts with and into an

EU-centralized consultation process. There was ambiguity about whether products in these higher-risk categories that are marketed under current EU directives would need to be considered for this scrutiny process simply as a result of modifications made in conjunction with the oncoming MDR. The verdict from this latest guidance is "no."

Progress in the Netherlands: Policymakers in The Hague are pushing forward with legislation and a decree necessary to officially implement the MDR and IVDR in the Netherlands. Each member state must separately implement the EU-wide rules, and it appears the Netherlands is among the most efficient countries in making this happen. The country's House adopted a Medical Devices Act in April and the Senate issued a preliminary report on the bill May 21, while collecting public comment on a decree that addresses various issues where individual countries have some leeway, such as rules for reprocessing of single-use devices and the implant card that must be provided to patients with a new implant, according to Netherlands-based attorney Erik Vollebregt.

What's Next, and Other Things to Worry About

Eyeing implementing acts and guidance: EU policymakers are apparently hard at work in producing both guidance documents and what are called implementing acts and delegated acts, which are necessary to translate the base regulation into practice throughout each EU member state. While several acts and guidelines have been issued, many more remain in the works, for both the MDR and IVDR. For instance, the commission says it is working on an implementing act to establish the expert panels and labs that will be necessary to conduct the scrutiny process for high-risk devices and diagnostics, and it plans to have it complete by September. Dozens of other acts and guidelines are in the works, some with clearer timelines then others.

Brexit: In April, EU leaders granted the UK an extension on its planned exit from the Union until October 31. That gives companies a little more time but does not resolve any ambiguity about the post-Brexit environment. If the UK makes a clean (no-deal) split, device firms would need to contract with a (non-UK) EU-based notified body to sell on that market, and they would need to secure an "authorized representative" within the new EU borders.

But, currently, about 50% of devices currently sold in the EU went through one of the four big UK-based notified bodies. Several of those organizations have taken steps to establish headquarters outside of the UK. BSI was ahead of the pack in establishing a home in the Netherlands and is now formally transferring UK-based certificates to the new location. But not all devices will necessarily be able to find a new EU home in time, particularly as notified bodies are also struggling to get designated under the new MDR and IVDR.

Under a no-deal Brexit, the UK is prepared to adopt regulations that would mirror the EU MDR/IVDR, but companies would still be required to register separately with the UK regulator. Of course, it's possible the EU and UK will reach a deal before the end of October that allows the UK to remain EU regulatory structure, but the current level of ambiguity is high.

Wilkinson departure: And, meanwhile, an additional exit, of sorts, has been added on for the end of October. John Wilkinson, who heads the devices branch of the UK regulatory (the Medicines and Healthcare products Regulatory Agency, MHRA), announced on May 1 his plans to retire at that time. Wilkinson has been with MHRA since 2012 and before that led MedTech Europe forerunner Eucomed. He is highly respected not just in the UK, but EU-wide, as a regulatory expert and steady hand, so his departure is a cause for more anxiety by some in industry during this unstable period.

Swiss snag? And the UK isn't the only country that is risking regulatory complications with the EU. Switzerland is not part of the EU but has long worked under a mutual recognition agreement (MRA) that has allowed for free flow of goods and harmonized regulations. But in an April letter, the Swiss Medtech industry association says renewal of the MRA is in doubt, and, thus, Switzerland-based manufacturers should be ready to approach the EU market as a "third country," including securing an authorized representative in an official EU country.

Medtronic and Blue Cross and Blue Shield of Minnesota Partnering to Impact Diabetes Outcomes—with Industry-First Performance-Based Rebates

>>Tracy Schaaf

Medtronic plc and Minnesota's largest health plan, **Blue Cross and Blue Shield of Minnesota** (BCBSMN), are working together in a first-of-its-kind, outcomes-based agreement in which Medtronic will pay patients using its new *Guardian Connect* smart Continuous Glucose Monitoring (CGM) system who don't see their blood sugar levels stay within an acceptable range. With this incentive-based agreement, and other partnerships—including a recent performance guarantee tied to its *MiniMed 670G* self-adjusting insulin pump—Medtronic is putting its money where its mouth is in terms of containing costs, and improving health outcomes and quality of life for one of the world's most costly chronic diseases: diabetes.

In early April, Medtronic and BCBSMN announced the agreement that provides BCBSMN members living with diabetes improved access to the *Guardian Connect* smart CGM system (FDA-approved last March). Using the amount of time spent in a healthy glucose range as a key metric, value-based payments will be tied—also an industry first—to the percentage of Time in Range (TIR) achieved using the system. TIR is a performance metric that tracks the amount of time a person's glucose is in their optimal range, with 70-180 mg/dL being the standard. Staying within the TIR parameters helps insulin-dependent diabetic patients minimize both short- and long-term health complications from dangerously high or low glucose levels. TIR is being increasingly adopted as a metric within diabetes management, said Pamela Reese, a spokesperson for Medtronic in a recent interview with *Market Pathways*.

As part of the agreement, BCBSMN members using the *Guardian Connect* or the *MiniMed 670G* insulin pump system are able to participate in the social- and gamification-based Medtronic Inner Circle patient engagement program. Members who participate can earn points and offset up to $300 a year in out-of-pocket costs by completing certain activities or achieving monthly TIR goals.

"We believe that outcomes-based agreements have the potential to provide an opportunity to create value for the member," said Mark Steffen, MD, Vice President and Chief Medical Officer at BCBSMN, in comments to *Market Pathways*. "We aim to transform the current healthcare model that incentivizes illness instead of wellness and we will continue to seek out innovative partnerships to make that happen."

Medtronic and BCBSMN employed a unique, patient-focused approach in designing the partnership. "Our companies brought our business stakeholders/owners into the story telling, inquiry, and empathy building process with patients and caregivers—this is extremely rare," said Steffen. "We had face-to-face sessions with patients and members who have diabetes as well as caregivers to hear firsthand the day-in-the-life stories and experiences in an authentic way. The Blue Cross team elevated this work by literally putting ourselves into it and wearing the device, doing the finger stick tests, and tracking our food intake. This level of emersion and shared understanding took time, investment, and vulnerability."

The *Guardian Connect* is the first smart standalone CGM system that can predict future high and low glucose events up to 60 minutes in advance, for people 14 to 75 years old. It also includes exclusive access to the artificial intelligence-based technology, *Sugar.IQ* smart diabetes assistant. *Sugar.IQ*, developed by **IBM Watson Health**, continually analyzes how an individual's glucose levels respond to their food intake, insulin dosages, daily routines, and other factors. In addition,

the *Guardian Connect* is the first and only standalone CGM system approved to send continuous sensor glucose data directly from the sensor transmitter to a smartphone, without requiring an additional receiver. It has been available outside the US since 2016.

BCBSMN also reclassified the *Guardian Connect* system as a pharmacy product instead of durable medical equipment, which means that some members with traditional copay plans will pay less for the monitor and disposable sensors. (Members often reach out-of-pocket spending caps for drugs long before they hit personal spending caps on medical equipment. BCBSMN will continue to offer other CGM devices on their plan in addition to the *Guardian Connect*.)

This isn't the first time that Medtronic has assumed risk and tied rebate payments to its diabetes devices. The firm initiated outcomes-based agreements with **UnitedHealthcare Group** in 2016 and with **Aetna Inc.** in 2017. And in June of last year, the company launched its *MiniMed 670G* Performance Guarantee Program—an outcomes-based offering to payors and employers in which the company provides flat-fee reimbursements up to $25,000 per pump over four years for qualifying diabetes-related inpatient hospitalization and emergency room admissions for eligible in-network patients in the US. The *MiniMed 670G* system, featuring the company's *SmartGuard* and *Guardian Sensor 3* technologies, is the world's first self-adjusting insulin pump that delivers personalized amounts of basal insulin every five minutes based on real-time sensor glucose values. *SmartGuard* technology is the only algorithm with the ability to reduce the risk of hypoglycemia by 44%, stabilize glucose at recommended levels, and minimize blood sugar variability.

Medtronic plans to work with additional insurers on similar innovative outcomes- and incentive-based agreements as part of the company's overall commitment to value-based care, said Reese.

Should You Throw the Least Burdensome Flag?

Companies are being offered a new remedy by FDA when they feel the agency has gone too far in its 510(k) requests.

>>David Filmore

Regulatory officials at device firms have started to notice some new language included in 510(k) "additional information" (AI) letters in recent months, offering sponsors the opportunity to "throw the least burdensome flag."

Referencing a penalty flag in American football, FDA has quietly launched the new program that allows companies to request an informal review by upper management if they feel deficiencies cited in an AI letter go beyond what regulations require. It is intended to take the place of a more formal, and potentially time-consuming, appeals process.

"The goal of a least burdensome flag is to quickly address FDA requests that submitters do not believe are least burdensome or when the submitter believes they are being held to a different standard than the legally marketed predicate device," according to letters sent in response to 510(k) submissions to company regulatory representatives.

The agency started including the language in all letters that are *not* potential "not substantially equivalent" decisions in March, according to an FDA webinar conducted that month. That step followed a small pilot conducted by seven review branches from February through September 2018. Two of 132 letters that included the new language in AI letters resulted in a flag being thrown. The feedback was positive and firms that did not take advantage of the offer said they would have if they needed it, according to FDA.

Flags must be thrown within 60 days of receiving a letter and they should be limited to two topic areas, FDA says. Before using the flag, sponsors should check with their reviewer or manager to see if even a quicker fix can't be found, the agency notes. To request a flag, sponsors should email their reviewer, the manager and 510(k) staff with their concerns and a proposed solution.

The flag option is part of broader efforts by FDA's device center to enhance its application of the least burdensome concept—the idea, first put into medical device statutes in 1997, that FDA should ask for the least amount of information necessary to fulfill regulatory requirements. The agency has recently enhanced reviewer training and issued more guidance on its use of least burdensome in response to directives from Congress.

Aussie Regulatory Reforms Under Way

The TGA Launches an Action Plan for Medical Devices.

>>Tracy Schaaf

The impact of medical device regulatory reform and international harmonization is being felt in all corners of the globe, including Australia. In early April, Australia's Therapeutic Goods Administration (TGA) announced the "Action Plan for Medical Devices," a national plan that includes strategies for improving how new devices get on the market, to strengthen monitoring and follow up of devices already in use, and provide more information to patients about the devices they use. In addition, as other stakeholders are doing throughout the world, the Australian TGA is also preparing for the impact of Brexit on its medical device market.

The overall goal of the Australian reforms is to strengthen the country's regulatory system, and to ensure timely access to innovative new technologies while striking a balance with effective and appropriate scrutiny of these technologies. Regulators also plan to continue to be patient-focused and have greater transparency. The TGA has an aggressive timeline in place to establish working groups, complete stakeholder consultations, draft all regulatory changes, increase the capacity of its medical device review teams, and introduce legislation to implement changes, all by year-end 2020.

Under the Action Plan, regulations will be expanded to cover novel devices with software or digital components, including 3D-printed devices, diagnostic artificial intelligence (AI) systems, and software apps. The TGA will update the assessment process to address device cybersecurity risks, and offer guidance on associated requirements for information technology (IT) systems. For higher-risk devices, the TGA will consult on whether the government should require greater levels of scrutiny of clinical evidence for certain groups of devices. These include spinal implants, devices that make diagnoses, diabetes management devices, *in vitro* fertilization devices, and companion diagnostics.

Under the Action Plan, TGA first of all wants to improve how new devices get on the market, with a focus on more rigorous assessment processes; more reviews of low- and medium-risk devices; higher level scrutiny of clinical evidence; and assurance that new and emerging technologies are safe. A second goal is to strengthen monitoring and follow-up of devices already in use. Efforts along these lines will include: scope the introduction of unique device identifiers; enhance inspections and reviews to confirm ongoing quality and safety; explore removing reporting barriers including potential of mandatory reporting of adverse events by healthcare facilities; and greater data analysis, information sharing and coordinated hospital systems.

A third focus of the Action Plan will be to provide more information to patients about the devices they use by publishing more information about decisions made and the devices regulated by the TGA;

strengthening consumer awareness of how safety and performance of medical devices are assessed; finding and implementing ways to help consumers report adverse events more easily; and establish expert groups with consumer representation.

Australia's reform plan follows the FDA's update to its April 2018 medical device safety action plan last November. It also came in the wake growing scrutiny on global oversight of device safety, in particular the November 2018 "Implant Files" investigation by the International Consortium of Investigative Journalists.

Greater transparency is a cornerstone of the action plans from TGA, Health Canada, and FDA. These countries are all members of the International Medical Devices Regulators Forum (IMDRF), a voluntary group of device regulators from around the world working to accelerate international medtech regulatory harmonization and convergence. Other member countries include Brazil, China, Europe, Japan, Russia, Singapore, and South Korea.

The Impact of Brexit

Australia relies heavily on imported medical technology (*see Figure 1*), and more than 90% of medical equipment is approved based on a European CE certificate. The Australian TGA, like other countries around the world, is preparing for the impact of Brexit on its medical device market.

> *AUSTRALIA'S REFORM PLAN FOLLOWS THE FDA'S UPDATE TO ITS APRIL 2018 MEDICAL DEVICE SAFETY ACTION PLAN LAST NOVEMBER.*

TGA announced in March that if a no-deal Brexit comes to pass, it plans to continue accepting conformity assessments from UK-based Notified Bodies for devices currently listed in the Australian Register of Therapeutic Goods (ARTG) as well as for new market applications. ARTG-listed devices may still be marketed in Australia using current CE mark certifications issued by UK Notified Bodies, and subject to UK Medicines and Healthcare Products Regulatory Agency (MHRA) oversight.

As an alternative, if UK and EU authorities agree to an orderly Brexit, recognition of UK-based Notified Bodies will remain in place through 2020. Device certifications from these Notified Bodies will continue to be accepted by TGA for ARTG listing. In January, the Australian and UK governments established a Mutual Recognition Agreement that addresses issues including recognition of certifications and conformity assessments, which will provide additional continuity measures for some types of devices in Australia.

Figure 1

Australian Medical Device Market at a Glance

>>More than 500 companies are generating total revenue of A$11.8 billion, exporting over A$2.1 billion each year to more than 160 different countries around the world, and employing over 19,000 people.

>>The medical technology industry produces more than 53,000 medical devices listed on the Australian Register of Therapeutic Goods (ARTG).

>>The majority (54%) of Australian medical device and diagnostics companies have grown from start-ups. Over one-third (35%) are established as a subsidiary of a multinational company.

>>40% of all medical device businesses have been established since 2000.

>>The top 10 destinations for Australian medical devices and diagnostics exports are the US, New Zealand, the United Kingdom, Germany, the Netherlands, Japan, China, Singapore, Denmark, and the Republic of Korea.

>>Australia is the eighth largest market for US exporters of medical products. In 2017, US exports of medical equipment and supplies to Australia totaled $1.5 billion, representing 3.5% of total medical equipment and supplies exports.

Sources: Australian Trade Commission (Austrade); Australia Department of Health; the Medical Technology Association of Australia (MTAA); the International Trade Administration (US Department of Commerce)

Oldies But Goodies?

Device Groups Pan FDA's Proposal to Underscore Older Predicates

FDA wants to upgrade the 510(k) program to better accommodate modern technology. But industry says the program is already plenty flexible, and the agency's ideas to invite public scrutiny of older predicate devices or even restrict their use are misguided.

>>David Filmore

FDA can't get much love for its 510(k) reform proposals of late. Of most recent note, it is difficult to find any group or individual supporting the agency's idea to help "modernize" the pre-market clearance program by creating a public listing of 510(k)-cleared devices that rely on predicate devices that are more than 10 years old, or any other age-based threshold.

Device director Jeffrey Shuren and then-Commissioner Scott Gottlieb floated the concept last November and FDA issued a formal comment request, which also asked for other ideas to improve the 510(k) program, in January. FDA also suggested it was weighing whether it needed new authorities to make "at least some older devices ineligible as predicates" and to streamline its ability to upclassify or add special controls to marketed device categories.

The agency was careful to explain that it did not believe that older predicates are inherently less safe, but that the fact that nearly 20% of current 510(k) devices rely on predicates older than 10 years suggests that some devices "may not be continually improving, which is the hallmark of health technologies." The agency's theory is that putting devices that rely on older predicates on a public list might nudge some companies to seek new clearances based on updated predicates.

Soon after FDA floated the idea, industry regulatory experts and attorneys started suggesting it was misguided, and that sentiment is well-represented in written comments submitted to FDA (as of a May 22 comment deadline). Just about all organizations and companies that submitted comments threw cold water on the proposal. (The other main tranche of comments came from individuals injured by a particular device calling for a complete overhaul or repeal of the 510(k) program.)

The fundamental arguments forwarded against FDA's proposal are:

1. The age of a predicate is an arbitrary way of judging its appropriateness and the time period for considering a predicate outdated can vary significantly from product to product.

2. In many cases, an older predicate *is* the best comparator for a device, even if newer devices are available on the market.

3. A public listing as proposed might unfairly paint products as inferior in the minds of patients, and it could encourage firms to remove certain well-established older devices from the market.

Ruey Dempsey, VP of Technology and Regulatory for AdvaMed, argues in the group's letter to FDA that putting focus on the age of the predicate doesn't account for all the considerations that must go into a 510(k) submission and review.

"When a device incorporates technology that is different than that of the cited predicate(s), the company is required to demonstrate that the new technology does not raise different questions of safety and effectiveness and that there are valid scientific means to evaluate the effects of changes in technology," she writes. "This requirement is met when the company provides data to demonstrate the safety and effectiveness of the new device. FDA does not determine substantial equivalence solely on the comparison of the new device to the technology of the older predicate."

She points out that many older devices remain relevant as predicate devices "because they meet current standards of care, represent a more affordable option than the latest technology and are well understood by the user."

Posting a list of devices that rely on older predicates could raise multiple unintended questions, according to Stephen Ferguson, chairman of device-maker Cook Group in its letter to FDA. For instance, Ferguson wonders, would health insurers misinterpret the list and use it to rationalize non-coverage decisions and would liability insurers decide not to cover impacted devices for manufacturers or healthcare providers?

Jeffrey Shapiro, a regulatory attorney with Washington, DC-based Hyman Phelps & McNamara, pointed out, based on analysis he and colleagues have conducted, that a good proportion of the 20% of devices cited by FDA that rely on a predicate older than 10 years also cited at least one product under 10 years, so it is hard to say that those are not relying on updated technology. (Companies can use a primary predicate and additional reference devices to help make a substantial equivalence claim.)

"If a device type has been evolving rapidly, a submitter always has an incentive to choose the most up-to-date predicate possible in order to take advantage of FDA's prior clearances and reduce the data burden," Shapiro wrote to FDA. "That is why our review found a strong natural slant toward more recent clearances. There are some device types that may not evolve rapidly. In these cases, there is nothing pernicious about reaching back to older predicates. It may be somewhat misleading in such cases for FDA to suggest that there is."

Mark Leahey, president and CEO of the Medical Device Manufacturers Association, made a fundamental argument against FDA's rational for the proposal—to encourage companies to adopt modern features in their devices. "Available evidence demonstrates that the pace of medical technology innovation and the robustness of 510(k) submissions has progressed unabated in the absence of agency action with respect to the age of predicate devices," Leahey wrote.

Even the National Center for Health Research, an organization that argues the 510(k) system is fundamentally flawed and should be replaced, told FDA that focusing on the age of a predicate was not the way to go. "The age of predicates is much less important than the many other shortcomings of CDRH's pre-market requirements and post-market surveillance," NHCR writes.

The feedback here follows the lukewarm response FDA received on its other major 510(k) reform initiative: to establish a new alternative 510(k) pathway that allows companies to use objective performance criteria (either guidance documents or consensus standards) to establish substantial equivalence rather than primarily on a comparison to a predicate device. FDA finalized guidance on this new "Safety and Performance Based Pathway" in January, but feedback last year from industry on a draft guidance questioned the benefit of the program and expressed concerns that FDA would frame devices cleared based on traditional predicates as second class.

Improve Online 510(k) Database, Payor Suggests

FDA also asked for ideas or alternatives to enhance the 510(k) program. Some of the feedback it received was simply to continue to educate stakeholders on how the 510(k) program works, to encourage sponsors to rely on the latest relevant predicate device, and for FDA to use its current authorities to up-classify specific device categories so they can no longer be predicates or employ "special controls" that add more testing or protections for targeted products, when appropriate.

But the Blue Cross Blue Shield Association, the only payor to contribute comments, floated some other interesting ideas. In particular, BCBSA argued that instead of creating a standalone list of devices cleared based on older predicates, FDA should improve the functionality of its current 510(k) database to make it easier for stakeholders to sort the information based on the most relevant characteristics for different device types.

"A user interacting with the complete list should be able to sort devices within a topic area based on the level of innovation within that topic area to ensure the user can make a meaningful comparison between products," Kris Haltmeyer, BCBSA's VP for Legislative and Regulatory Policy wrote. Users should also be able sort and filter devices based on the level of risk associated with a product area and whether there are safety signals linked to a device, he noted.

"We recommend the FDA proactively work to identify device areas where there have been safety signals and actively encourage innovation in these spaces," Haltmeyer said.

BCBSA also made the interesting proposal that FDA should publicly introduce "thresholds that are clinically meaningful" for establishing the validity of predicate devices. "We understand 510(k) applicants will vary in their designs, and we understand that these devices do not meet the need for a full

pre-market approval," the insurer wrote. "However, the importance of any FDA approval carries such significant weight that the criteria for establishing if a potential predicate device is valid should be transparent and consistently applied."

Device-maker **BTG plc** made a similar point in its feedback to FDA. "Further input into a decision to use a predicate should be considered and reported by the agency where applicable," the company wrote. "The context of the use of predicates should be clearly defined with reference to the treatment landscapes under which the products are intended to be used, and whether the predicates can be justified to be used in patients given other alternative (better, i.e., safer and effective) treatments."

What's Next?

FDA officials say they will closely review comments and are open to different ideas for how to modernize and enhance the 510(k) program. It seems unlikely that FDA will propose an action to directly limit use of predicates based on age any time soon. Marjorie Shulman, who oversees 510(k) policies at the agency, said at a recent meeting that a rigid policy to do so would be "awful."

In the meantime, the agency is preparing to release the first set of product codes that could be eligible for the new "Safety and Performance Based Pathway." And it appears to be having early success with a pilot program launched late last year that promises quicker reviews (60 days vs. 90 days) for certain products if a sponsor uses a standardized electronic submission form.

Other organizations that commented on FDA's recent 510(k) modernization plans include: Johnson & Johnson, the Medical Imaging & Technology Alliance (MITA), and the BRIDGE (Bringing Real-world Insight for Device Governance and Evaluation) Coalition.

Global Regulations: Updates from IMDRF

Officials from Brazil, Japan, South Korea, and Singapore spotlighted key initiatives during a recent gathering of the International Medical Device Regulators Forum.

>>David Filmore

The International Medical Device Regulators Forum met in March for its latest biannual meeting in Moscow. In addition to advancing work on an array of harmonization-focused documents, individual countries provided updates on regulatory efforts within their jurisdictions. Here were a few of the most interesting takeaways:

>>Brazil

In May, a new streamlined market pathway for low risk, Class I devices took effect. Qualifying products can enter the market via a simple notification to ANVISA, Brazil's regulatory authority, rather than having to undergo a "simplified approval" process.

>>Japan

At the start of 2019, Japan's Pharmaceuticals and Medical Devices Agency established a new unit specializing in medical devices with the goal of strengthening coordination between different device functions to improve efficiency, as part of a broader reorganization.

>>South Korea

Legislation is expected to be finalized in June to establish a new pathway for advanced medical devices and to streamline pre-market oversight of *in* vitro diagnostics. The "Medical Device Industry Promotion and Innovative Medical Device Support Act" and the "*In-Vitro* Diagnostic Device Act" are currently under review by Korea's National Assembly, according to Hyeonjoo Oh, director general for Korea's Medical Devices Evaluation Department.

>>Singapore

The country is launching a new online system for submission of recalls and field safety corrective actions for medical devices this month, according to Rama Sethuraman, acting director of the Medical Device Branch in Singapore's Health Sciences Authority.

Canada Device Application Fees

Set to Rise

Health Canada says it needs more support from industry to cover review costs. A new fee structure to meet that need is now set.

>>David Filmore

Device companies submitting product applications to Health Canada next year will notice some significant fee rises, though the regulatory agency moderated the size of the increases compared to a prior proposal.

Starting next April, firms may experience anything from an 8.6% rise (to $450, for relatively low-risk Class II device submissions) to a 77% increase for certain high-risk Class IV devices, according to a final report issued by Health Canada on May 15. The increases are based on a new fee-calculation structure that the agency says is necessary to cover its costs (drug fees are also on the rise); it's the first fee-structure change in Canada since 2011.

In addition to the rate increases, reforms to the fee structure include:

A provision that requires Health Canada to pay companies a rebate if the agency takes longer than pre-set performance standards for each application type (15 days for Class II devices; 60 days for Class III devices; and 75 days for Class IV devices).

Adding a "pause the clock" feature that allows performance-standard time when an application is in the hands of the agency (rather than sent back to a sponsor with questions).

A small-business allowance that would grant a free first submission to qualifying businesses and discounts thereafter.

Fees would be annually increased based on the consumer price index, rather than a flat annual increase.

While license application fees are ramping up, the annual establishment fees that companies must pay if they market Class I devices that don't require a license are dropping significantly—from a current fee of $8,438, down about 45% to $4,590. Also, so-called "right-to-sell" fees are dropping slightly to $381 next year.

Health Canada made its original proposals for the new fee structure in 2017, when it was asking for device application fees that would cover 90% of its costs. But in the final version, the agency is settling for fees that will phase in over four years to equal 75% of its estimated review costs.

Fee Type	Fiscal Year 2019-20	Fiscal Year 2020-21	Percent Increase	Performance Standard
Class II license applications	$414	$450	8.6%	15 calendar days to review
Class III license applications	$5,922	$7,477	26.2%	60 calendar days to review
Class III license amendment – manufacturing changes	$1,492	$1,903	27.5%	60 calendar days to review
Class III license amendment – significant changes not related to manufacturing	$5,546	$6,608	19.1%	60 calendar days to review
Class IV license applications	$13,770	$24,345	77%	75 calendar days to review
Class IV license applications (near patient in vitro diagnostic device)	$23,473	$24,345	3.7%	75 calendar days to review
Class IV license amendment – manufacturing changes	$1,492	$1,903	27.5%	75 calendar days to review
Class IV license amendment – significant changes not related to manufacturing	$6,319	$8,057	27.5%	75 calendar days to review

Source: Health Canada

JEFF SHUREN, 10 YEARS IN AT CDRH, Wants More Space to Innovate

>>David Filmore

Market Pathways checked in with Jeff Shuren as he approaches his decade mark at the FDA's Center for Devices and Radiological Health. The longest-serving director in the center's history, Shuren has so far left a vast and lasting footprint on how devices are regulated in the US. But he pines for a more untethered CDRH that can nimbly adapt itself to the rapidly evolving technology landscape.

Jeff Shuren, MD, ***a neurologist, joined CDRH as acting director in September 2009, and dropped the "acting" designation the following January. He first joined FDA in 1998 and served in various policy planning positions at the agency, in addition to a one-year detail in Congress and a stint at the Centers for Medicare & Medicaid Services from 2001-2003.***

Jeff Shuren, who was a big Star Trek fan as a kid, says he wants to "boldly take CDRH where it has never gone before." But, to his frustration, rigid statutes can sometimes get in the way of truly exploring the outer reaches of device regulatory strategies.

Shuren is coming up on 10 years leading FDA's Center for Devices and Radiological Health. He is now the longest-serving director of CDRH since the center was established in the early 1980s. And nobody would argue that it is has been a quiet tenure.

The volume of initiatives, pilot programs, frameworks, partnerships, and more that have rolled out of CDRH in the past decade has been striking. And the pace has only picked up in recent years. It has led to a marked shift in the way FDA approaches its medical device mission. In 2009, when Shuren joined CDRH, FDA, in industry's consensus view, was the place new technology went to languish, and Europe was the land of opportunity. That narrative has since been completely flipped on its head. This is the result in large part of big process and culture changes at Shuren's CDRH. At the same time, Europe currently finds itself in a bit of a morass as it struggles to implement new regulations. (*See "EU MDR: Welcome to the New Reality," this issue.*)

Industry often sings the praises of Shuren and his center, and its impact on speeding the path of innovation. And Shuren is clearly proud of the accomplishments and his team.

Market Pathways recently spoke with Shuren and asked him to reflect on his decade mark at CDRH. During the conversation he called CDRH's staff "the most public-health committed, forward-leaning, and innovative group of people I've had the honor to work with in government in my over 20 years of public service." They are the Enterprise crew to his Captain Kirk, he says.

Shuren identifies what he believes is the underlying cultural shift that has taken place at the center over his tenure: a move to a more "customer-service oriented" model. Patients are the most important customer, he stresses, and the fundamental way FDA addresses their needs is to improve timely access to safe, innovative therapies and diagnostics. Industry, "our biggest customer," benefits as a result of that patient focus in the form of a more predictable path to market, Shuren says. That is a different framing from playing a pure regulator role, in which the agency would view each new product submissions in a little bit more of a vacuum from the impacted patient community.

"Ultimately, our public health mission is about improving the health and the quality of life of patients," he said. "Industry has simply benefited as a result."

Emerging Tech Challenges FDA Framework

Still, despite the pride he takes in this evolving dynamic, Shuren has developed a fundamental frustration with his job. It is one that may be surprising to those who have witnessed the rapid—sometimes almost jarring—pace of CDRH policy developments in recent years, including a range of outside-of-the-box initiatives. His beef: things move too slowly, and the agency doesn't have enough flexibility to try new things, fail, and then refine.

"The medical device framework is over 40 years old and it was intended for a different world of technology," Shuren said in the interview. "While there have been tweaks made to the program over time by Congress, there have not been fundamental changes to deal with the truly unique issues we're dealing with and the emerging technologies that are coming before us."

"We have to be in a position where we are agile, or flexible—we're trying new things. Also, like any other innovator, we have to have the ability to fail, but to fail responsibly," he noted. "By that I mean, we're not going to do things that put patients at risk, but we have to be able to try some new things to see if they're going to ultimately benefit patients. If it doesn't work out, it doesn't work out, but we're never going to know unless we try."

> "WE'RE NOT GOING TO DO THINGS THAT PUT PATIENTS AT RISK, BUT WE HAVE TO BE ABLE TO TRY SOME NEW THINGS TO SEE IF THEY'RE GOING TO ULTIMATELY BENEFIT PATIENTS."
>
> **—Jeff Shuren**

And there is little question that Shuren and team are trying new things. CDRH has been issuing more policies of late that seem to creep up close to the bounds of its statutory authority. One example is the center's recently unveiled policy to create a new, optional 510(k) pathway, called the "Safety and Performance Based Pathway." It establishes a route to 510(k) clearance in which a device can be measured against established performance criteria captured in guidance or standards, rather than in a direct comparison to a predicate device, which has been the core element of 510(k) reviews for the past 40 years.

Another example is the center's pre-certification program for digital health software. Under that framework, FDA envisions performing "excellence appraisals" of companies that would validate the robustness of a firm's software design and development processes. As a result of having trust in the company's underlying processes, FDA would do a less detailed review (or, in some cases, potentially skip the review altogether) when each new software line and iteration is developed for market by that company. This more company-centered rather than product-by-product approach has also attracted FDA's interest in the diagnostics realm, and other areas.

These are examples of bold policy ideas within the frame of the device regulatory community. But FDA is necessarily pursuing them in a cautious manner.

For example, the alternative 510(k) pathway doesn't literally remove the predicate from the equation—the chosen performance criteria must "align" with the performance of a legally marketed device. In the case of the pre-cert program,

following an information-collecting pilot process in 2018, the center has embarked on a test plan where companies that make "software as a medical device" can agree to undergo an excellence appraisal. It put out a request for participants on May 22. Firms that volunteer would ultimately make a traditional submission to FDA, but an independent FDA review team would only be provided with the sections that would have been deemed necessary under the pre-cert program. They will assess whether it is enough to make a fully informed safety and effectiveness decision, and only be provided with

510(k) FOCUS

One central narrative and point of debate during Shuren's tenure has been the endeavor of "510(k) reform." There has been a continuous push and pull over the program between consumer advocates who have argued that it is a "fast track" that lets unsafe devices on the market and device companies who point to its "substantial equivalence"-based design as crucial to supporting the iterative nature of device innovation, and bristle at any signs that barriers are forming around the most common pathway to the US device market.

Complaints about the program from both sides were reaching a fever pitch when Shuren came to the center in 2009. That led him to contract with the Institute of Medicine to study the issue; and the IOM famously came back with a recommendation to get rid of the entire program. CDRH did not follow that recommendation. "I believe that eliminating the program with no appropriate alternative would have been irresponsible at the time, would have created chaos in the marketplace, and would have resulted in even fewer life-saving technologies being available in the US," Shuren tells *Market Pathways*.

Ultimately, the center made some changes to the program by updating its foundational guidance on substantial equivalence and, after fits and starts, its guideline on 510(k)s for device modifications, as well as other targeted guidance documents. The agency has also leveraged the flexibility of the 510(k) program to make it work for evolving technologies, Shuren argues. He points out, for instance, that the average number of pages in a 510(k) submission has increased by about 150% over the past decade, with more data required. But, at the same time, he says, the overall time-to-decision for 510(k)s has gone down due to efficiencies added to the process and more clarity and predictability about FDA's expectations. Also, Shuren has been making a point lately of emphasizing FDA's concerted efforts in recent years to "upclassify" devices to PMA level when a reassessment of safety and effectiveness evidence suggests the 510(k) pathway is insufficient.

Calls to abolish the 510(k) program have not ended. Just last month, the *New York Times* editorial board called on FDA to heed the IOM's advice "to ensure that no medical device intended for permanent residence inside a human body is used on patients without first being rigorously tested."

But Shuren argues the 510(k) program has evolved substantially in the past decade. And while 510(k) reform is still a focus at FDA, he makes the point that it has a different emphasis than it did when he first came to the center.

"Where we've moved in our early efforts to simply buttress an existing program to make sure that we're assuring devices are safe and effective, we're going to the next stage to say, 'Can we also drive the marketplace to not only make safe and effective devices but now safer, more effective technologies?' he explained. In other words, the center is trying to leverage the 510(k) program to nudge more firms to adapt to modern technological advancements.

Current reforms include, for instance, the newly defined Safety and Performance Based 510(k) Pathway that would base clearance on how a device measures against modern performance criteria, rather than by direct comparison to a predicate device.

"Companies can demonstrate they're substantially equivalent because they meet those performance criteria," Shuren said. "Unlike in a [traditional] 510(k), they not only can show that they meet them, they can show they can exceed them. We can start driving towards a more competitive marketplace around safer, more effective 510(k) technologies."

more of the submission if necessary. Ultimately, the agency has acknowledged that it will need to go back to Congress to implement some version of the program if it seems to work.

Seeking 'Regulatory Legos'

But that is the rub for Shuren. In his ideal world, the center could keep iterating until hitting a policy sweet spot for a product area. The lawmaking process is not friendly to that approach, he laments.

He raised the issue with some exasperation during a May panel discussion convened at the Food and Drug Law Institute (FDLI) Annual Conference. In digital health, for example, he said, "For years, we're looking at what to do, and then to go do it, is going to take years, in a field that's just rapidly evolving. That's crazy. That's nonsense, right? We cannot keep going back to Congress to change the law. There are nice people up there, but ...it takes forever, and you will not get what you want. That's the way it works.

"So, suppose instead, we have the ability, we have the agility, to really adapt what we do to emerging technologies, and not have to keep running back to Congress. That would be amazing, right? We could solve problems in real time. Not in lifetimes."

Shuren describes his ultimate goal to *Market Pathways* as "regulatory Legos."

"If I had my choice, ... I'd be able to craft a regulatory pathway without having to go back to Congress, that would be based upon the risk of the product. Then to be able, depending upon the kind of technology, select from a suite of regulatory options and kind of put that pathway together," he explained. "It's almost like I had a set of regulatory Legos, and I could build the pathway I needed to. So, Congress would give us the Legos, we would do the building. Whereas today, Congress has essentially built the pathways, and then we can make little tweaks around the margins."

THREE QUESTIONS for Jeff Shuren

We asked Shuren what he was most proud of, frustrated by, and what has taken him most by surprise during his decade leading the FDA device center.

>>Market Pathways: What are you most proud of from your work at CDRH?

Shuren: We have a number of important accomplishments under our belts, like increasing the annual number of device facility inspections we have access to through establishing the Medical Device Single Audit Program; increasing the annual number of novel devices granted marketing authorization in the US by more than four fold over the past decade—the highest numbers in the history of the program; being on the verge of launching NEST [the National Evaluation System for health Technology], creating IMDRF [the International Medical Device Regulators Forum] and the Medical Device Innovation Consortium.

I'd say what I'm most proud of, is the people at CDRH. They are, from my perspective, the most public-health committed, forward leaning, and innovative group of people I've had the honor to work with in government in my over 20 years of public service.

>>Is there a frustration or challenge that stands out for you?

The biggest frustration to me is that I wish we could do things more quickly. I wish we had the ability to just drive ... safe and effective technology out into the marketplace, and to do it safely. I'd like to see those benefits accrue to patients. I just wish we could do it more quickly.

>>What has most surprised you about CDRH and your role as director since you took the job?

When I started CDRH, I didn't have a good appreciation for the full spectrum of technologies and issues the center was handling, or even the volume of work the CDRH employees had to contend with. For example, the center receives over 20,000 submissions a year, and that includes meeting requests; [we review] about a million medical device reports each year. And the center approves about 12 new or modified devices every business day. It's truly remarkable and they do it all without the resources they should have. That's something I've found as a great surprise.

Piloting a Future

It is not clear if this vision is fully attainable. But it seems evident that CDRH is regularly pressing to do as much as it can with the building blocks it does have at its disposal. It also seems clear that policy proposals being floated around inside the center are several steps more creative than what ultimately gets released to the public.

"We are a pain in the butt in the FDA," Shuren acknowledged at FDLI. "We are pushing the chief counsel's buttons about, 'can we do this?' If they say no, we don't do it. But, yeah, we push the envelope as far as it can possibly go."

And that process within FDA, also "takes up an enormous about of time," he said. "We are pushing boundaries on semi-rigid lines. If we are going to be agile, we need an agile regulatory framework."

It is not easy to tell if Shuren has a strategy in mind to reach a point where his center has at least a few more regulatory Legos at its disposal, or if he views it more as a pipe dream. When asked whether he envisions attaining something closer to that reality during his tenure at CDRH, he jokes, "Well, I hope so. I wasn't planning to do this in the afterlife."

But later in the conversation, asked if there are specific things to be done or reforms to be made to allow CDRH to do things more quickly, he joked: "Oh, sure. I'd love to have that kind of a world. You'd have to give me the power over several branches of government. I don't think the Constitution allows for that."

What is clear is industry should expect more medtech policy experimentation coming out of the device center. And that could often come in the form of more pilot programs—an approach CDRH is increasingly using to float novel, outside-of-the-box ideas and to make best use of limited resources.

Further down the road, it might be interesting to observe FDA's approach during the next round of user-fee negotiations (in 2022), where it could have the opportunity to seek legislative reforms that would give it more regulatory flexibility than it currently has.

For now, Shuren shows no sign of slowing down CDRH's attempts to explore the frontier of device regulatory policy. But, unlike James Kirk, he won't have "warp speed" in his toolbox any time soon.

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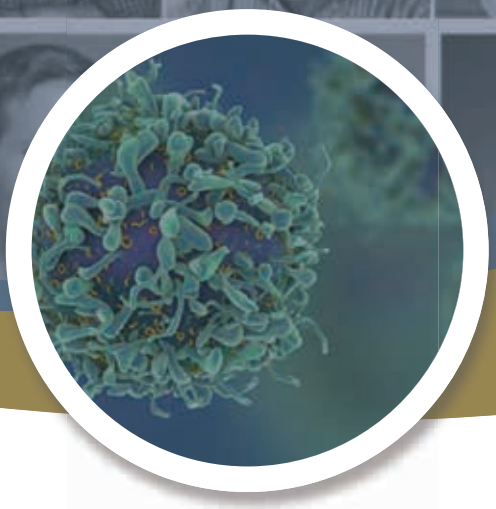
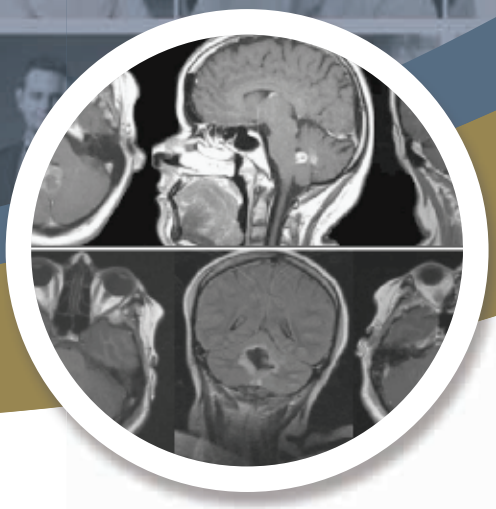


MedTech History

Discover the origin of cutting-edge medical device innovations



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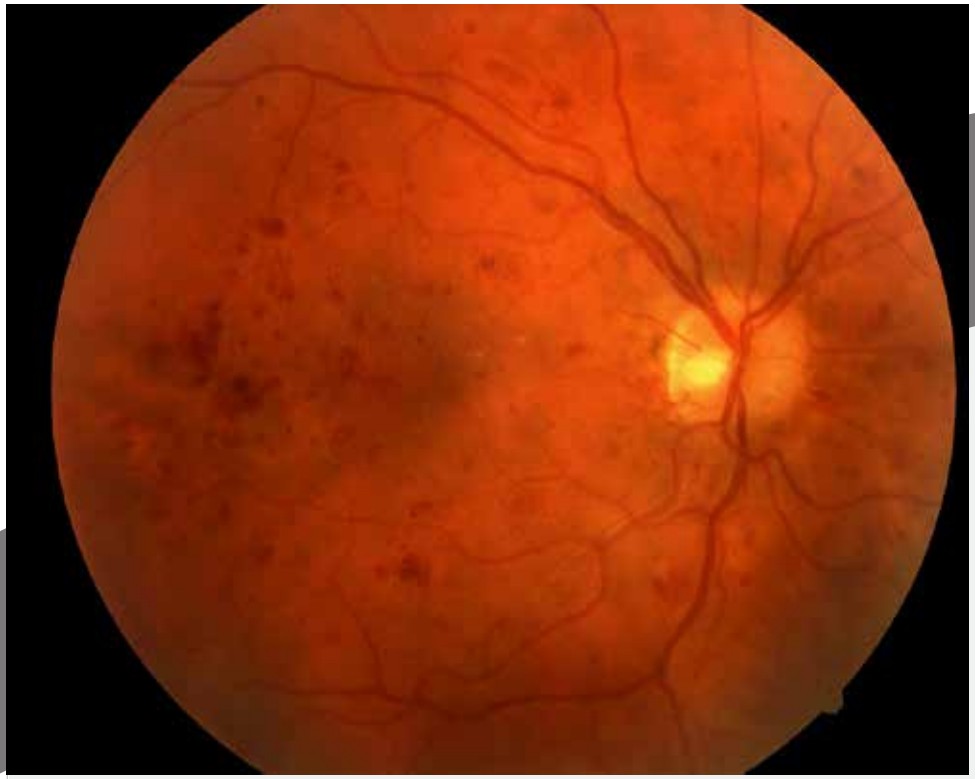

IDx Technologies: AI MEETS MARKET ACCESS with a Breakthrough Diabetic Retinopathy Detection Device

Each year, more than 24,000 Americans go blind from diabetic retinopathy. IDx Technologies, led by pioneering scientist, physician, and entrepreneur Michael Abramoff has been on a decades-long quest to prevent this devastating outcome with a first-of-its-kind, low-cost, autonomous artificial intelligence diagnostic system. With one of the first devices to gain approval via FDA's Breakthrough Device Program, the company is also helping to forge a new FDA pathway for AI in medtech, and it is pursuing a more AI-targeted reimbursement model, including a new CPT code.

>>Tracy Schaaf

More than 30 million Americans have diabetes, and an estimated 24,000 lose their vision each year from diabetic retinopathy (DR), the most common form of eye disease in these patients and the leading cause of blindness in working-age Americans. If caught early, vision loss is almost entirely preventable, yet only about half of people with diabetes get regular eye exams, according to the American Diabetes Association. With diabetes reaching epidemic proportions, the number of people in the US suffering from DR is expected to grow from 7.7 million now to more than 14 million by 2050, according to the Centers for Disease Control and Prevention. Globally, 640 million people (one in 10 adults) will have diabetes by 2040, with a third having DR. There is a huge unmet clinical need around the world, including in developing nations, for increased patient access to high-quality, affordable, point-of-care, early DR detection, in any care setting—not just an ophthalmologist's office—and by any healthcare provider.

Artificial intelligence (AI)—an emerging field that is beginning to move the needle on disease detection, personalized medicine and other areas within healthcare through the power of data—may hold the key to eliminating preventable blindness due to DR for good. **IDx Technologies Inc**., based in Coralville, IA, has spent the last decade developing a first-of-its-kind, inexpensive, AI-based diagnostic system, the *IDx-DR*, that detects DR autonomously without needing a physician to interpret the images or results. The groundbreaking system was not only one of the first to be approved via FDA's Breakthrough Device pathway, but it is also helping to forge

a new FDA regulatory route for AI in medtech. And, to further prove that it is a company undeterred by challenges, it is also pursuing a new CPT code.

Eye-to-Eye with FDA: IDx Helps Agency Gain Comfort with AI

IDx was founded in 2010 by American ophthalmologist, computer scientist and entrepreneur, Michael Abramoff, MD, PhD. Abramoff is the Robert C. Watzke Professor of Ophthalmology and Visual Sciences, as well as a Professor of Electrical and Computer Engineering and a Professor of Biomedical Engineering at the Roy J. and Lucille A. Carver College of Medicine at the University of Iowa. For the past 20 years, Abramoff has studied how AI algorithms can be used to detect disease in medical images, with a goal of lowering healthcare costs. He is the author of over 300 peer-reviewed publications, and the inventor of 16 issued patents and many more patent applications.

Abramoff experienced a career-defining moment as a resident, when he saw one of his patients with diabetes—a portrait painter who had irreversibly lost most of his sight due to DR. "It really impacted what he was able to do. Given my background in algorithms and machine learning ... I thought we should be able to do this better, and get earlier diagnosis for people with diabetic retinopathy," he told *Market Pathways* in a recent interview. "For many years we've known that that's the most important thing you can do for diabetes. People with diabetes care more about not going blind than dying or losing a limb."

When Abramoff founded IDx, he immediately started discussing with the FDA what he wanted to do: prove the safety, efficacy, and equity of autonomous AI. This concept of a medical technology that makes a clinical decision by itself, with no human oversight, was new for the agency and they were initially very skeptical, he says.

"They needed to know how we planned to make sure [that our technology] is safe and efficient and equitable; meaning does it work equally well for all groups of people with diabetes ... all races, ethnicities and ages." IDx had many discussions with FDA over the years as they and the team co-developed these important principles, which also included cost efficiency, and situations in which AI is right and the clinician is wrong, he explains. "They used a lot of resources to work with us because [autonomous AI] was entirely new for them."

Working with the FDA can be intimidating at first, and the agency is portrayed as a huge obstacle, Abramoff says. "But, they're just incredibly rigorous people, trying to make sure everything's safe and works. But it's also qualifying, as it establishes a high standard of proof."

Autonomous AI has huge potential for healthcare savings, improved quality, and improved access, especially in the areas of imaging, diagnostics, and predictive analytics. However, Abramoff warns against losing those potentials if developers and regulators move too fast and cut corners. "We've seen it in earlier self-driving cars, where there was a deadly accident a year ago, and [developers] pulled back because they said,


MICHAEL ABRAMOFF

'Well, we didn't realize that people would be dying,'" says Abramoff. "So what does that mean for a medical device, where somebody's health and life could be threatened?"

Accountability and transparency about the benefits versus the risks of a technology are very important, he explains. "I think it's important that we always place the patient central, both benefit and potential risk of harm to the patient ... we shouldn't lose sight one from the other."

FDA is taking steps to develop a framework for regulating AI products used in medicine, in particular those that continually adapt and improve based on real-world data (*see sidebar, "A New Frontier for FDA: Adaptive AI.*). (IDx's system uses "locked" and validated algorithms that don't continually adapt or learn every time they are used, but instead are modified by the company.)

Finally, after nearly a decade of development, Abramoff and his team conducted the first-ever preregistered clinical trial for AI, and proved that their technology was safe, equitable, and efficient. "It was pretty exciting, because it hadn't been done before," he says.

In April of last year, only two months after its submission, the FDA cleared the way for IDx to begin marketing its *IDx-DR* device, the first ever autonomous AI system to be able to detect greater than a mild level of diabetic retinopathy in adults who have diabetes, with immediate diagnosis at the point of care. *IDx-DR* is a software program that uses an AI algorithm to autonomously analyze images of the eye taken with a retinal camera, the *Topcon NW400*. A staff member with several hours of training captures two images per eye with the robotic camera using *IDx-DR*, while receiving guidance to take good image quality from the AI system. Within seconds, the AI system produces an immediate diagnostic report at the point-of-care that includes a disease output and follow-up care instructions. No review of the images by a human expert is needed.

Once sufficient image quality is achieved, patients receive one of two results: negative for more than mild diabetic retinopathy, retest in 12 months; or more than mild diabetic retinopathy detected, refer to an eye care professional.

IDx-DR was reviewed under the FDA's De Novo premarket review pathway, and in addition, it was one of the first devices to be granted Breakthrough Device designation, which is reserved for technologies that "provide for more effective treatment or diagnosis of a life-threatening or irreversibly debilitating disease

A New Frontier for FDA: ADAPTIVE AI

The FDA has taken the first step into regulating the new and rapidly evolving world of AI medical technologies, starting first with devices that rely on so-called "locked algorithms." These systems, of which IDx's *IDx-DR* is an early example, do not change each time an algorithm is used, but instead are changed by a manufacturer at intervals, using specific training data and a validation process to ensure proper functioning of the system. Another example is **Viz.AI Inc.**'s *Viz.ai LVO Stroke Platform*, a computer-aided triage software approved by the FDA in February 2018 that analyzes images for indicators associated with stroke using an AI algorithm. (Viz.ai is backed by former Google CEO Eric Schmidt's venture capital firm, Innovation Endeavors, and Danhua Capital).

In early April, FDA announced that it is exploring the next step: developing a total product lifecycle approach to regulating a new generation of innovative AI medtech products that continually learn and adapt in real-time, based on new user data. Soon before leaving the agency, then-Commissioner Scott Gottlieb, MD, released a statement and a discussion paper that describes FDA's proposed approach to establishing careful oversight over this rapidly evolving segment.

"With artificial intelligence, because the device evolves based on what it learns while it's in real-world use, we're working to develop an appropriate framework that allows the software to evolve in ways to improve its performance while ensuring that changes meet our gold standard for safety and effectiveness," Gottlieb said. "It would be a more tailored fit than our existing regulatory paradigm for software as a medical device."

The review may examine the underlying performance of a product's algorithms, a manufacturer's plan to make modifications, and the manufacturer's ability to manage the risks associated with any modifications. The discussion paper is the first step in a months-long process in which the FDA is collecting feedback from the public and a variety of stakeholders in medicine (by June 3rd) before finalizing a policy on regulating adaptive AI systems.

or condition." In Abramoff's view, and although he hadn't been through the FDA process before, having the Breakthrough Device designation allowed the FDA to spend a lot of time and effort on IDx.

For the approval, FDA evaluated data from a 2017 US pivotal preregistered clinical trial of retinal images obtained from 900 subjects with diabetes at 10 primary care sites. The study, with results announced last March, was designed to evaluate how well *IDx-DR* could accurately detect patients with more than mild diabetic retinopathy. The AI system was able to correctly identify the presence of more than mild DR 87.4% of the time and was able to correctly identify those patients who did not have more than mild DR 89.5% of the time—both well above the superiority benchmarks set by the FDA.

Abramoff offers his candid advice to device companies that might be following the Breakthrough Device pathway, with any technology. "My first recommendation is not to be first, because it's a long, long route, and full of pitfalls and painful moments, we're learning ... so if you can avoid being the first, it's all good." Also, he recommends finding the best regulatory consultants that you can, to educate and guide you through the long and complex process.

He also recommends discussing very carefully with the FDA how you can prove that your technology is safe, equitable, and efficient. "If you don't do this well, you will have a mess on your hands, possibly after the clinical trial. The FDA wants to help, right?, They are there for you. So, meet with them early and often. They're not there to block you. They're trying to make it work, so if you take the more collaborative approach, that really helps. The support we got was amazing."

Investor Support and Launch Strategy

Since receiving approval, IDx has been ramping up implementation of its now-industry-standard *IDx-DR* system, with the assistance of a $33 million round of financing raised in September 2018. The financing was led by venture capital firm 8VC, with participation from Optum Ventures, Alpha Edison, and Heritage Provider Network. The financing was reportedly one of the largest start-up funding rounds in Iowa's history.

"At 8VC we bet on founders," says Drew Oetting, a founding partner at 8VC, in a recent conversation with *Market Pathways*. "Dr. Abramoff is incredibly rare in that he's a world-respected clinician in addition to a computer scientist, and that's why

Progress on this front will be discussed in upcoming issues of *Market Pathways*.

"Artificial intelligence has helped transform industries like finance and manufacturing, and I'm confident that these technologies will have a profound and positive impact on healthcare," Gottlieb wrote in his statement.

At the Food and Drug Law Institute (FDLI) annual conference on May 3 in Washington, DC, a panel of prominent FDA, legal, and device industry executives spoke to a packed audience about their thoughts on the FDA discussion paper. Panelists included Bakul Patel, Associate Director of Digital Health at CDRH; Carla Cartwright, Director of Global Regulatory Policy at Johnson & Johnson and member of the FDLI Board of Directors; Mark Levy, Partner at Eckert Seamans Cherin & Mellott; and Wade Ackerman, Partner at Covington & Burling LLP.

The four primary goals of a responsible AI regulatory framework within the FDA, according to Patel, include: 1) enhance patient access to high-quality digital medical products; 2) enable manufacturers to rapidly improve software products with minor changes; 3) maintain a reasonable assurance of safety and effectiveness; and 4) provide a minimally burdensome regulatory framework. Patel discussed IDx's technology and its De Novo/Breakthrough device approval as a "poster child" for where medtech AI and the standard of healthcare is trending.

In commenting on FDA's discussion paper, J&J's Cartwright emphasized that industry is very much aligned with the agency's goals. "We as manufacturers very much want a system that is risk-based, predictable, proportional, and innovation-friendly," she says. Johnson & Johnson is using AI and machine learning across the board, in everything from drug discovery to consumer products to precision surgery, she explained. "We also have to think beyond FDA to data issues like homeland security, cybersecurity, and AI ethics."

"Because of the uniqueness of artificial intelligence, with the software as a device, we have to look at how it is going to change the practice of medicine, as well as legal liability," added Levy. "All of this policy development is happening live now at FDA and on the Hill. It will have real implications for health data and life sciences companies," said Ackerman.

Technician performing diabetic retinopathy exam with IDx's *IDx-DR* system

he's the undisputed leader in bringing machine learning and autonomous decisioning into real clinical practice."

IDx is busy executing its market strategy: bringing *IDx-DR* into hospital and other healthcare systems so that it can benefit patients. It is working closely with endocrinology clinics, internal medicine clinics, diabetes education centers, diagnostic labs, community health clinics, and diabetes research groups nationwide to bring its system online while ensuring coordination between electronic health record (EHR) systems and facility workflow. Healthcare providers who are currently testing for DR may find *IDx-DR* to be a valuable tool to increase efficiency and patient throughput. And, with *IDx-DR* increasingly being used in the primary care setting, patients are able to get to ophthalmologists earlier in the disease state, and there is a better chance of treating blindness, according to the company.

"It's rewarding as we can finally get the technology to patients. I became a doctor for a reason, right?" says Abramoff. "It's very rewarding to see IDx systems in the wild, helping to prevent blindness, all while saving our society money and allowing clinicians to focus on higher order care delivery," says Oetting.

IDx is focusing first on launching in the US in order to prove and qualify for, in Abramoff's words, "the highest pinnacle of safety." The company also has approval to sell its system in Europe, is exporting *IDx-DR* to Japan, and is planning to enter other countries, including Brazil. "It makes a huge difference in Japan that we are FDA cleared, that they really think this is the highest standard to meet for all AI in healthcare," Abramoff says.

The company also plans to deploy its DR detection technology in low-income countries, where there is a severe lack of trained eye care professionals and services. "The whole point is making healthcare more affordable and having better access, and one of the points is in the developing world, which is greatly needed," says Abramoff.

IDx plans on putting the power of its AI technology to work in the early detection of other high-cost, highly prevalent medical conditions such as macular degeneration, glaucoma, ear infection in children, and Alzheimer's disease. The company is currently in discussions with FDA about multiple additional products with the goal of getting them through clinical trials.

And, now that IDx has forged a pathway to the US market, Abramoff expects additional AI medical devices to be approved very soon. "The exciting thing is that there will be many more of these, for many more diseases and conditions. The fact that we created this path that is now more clear, rather than reinventing it every time, that is very important for the FDA."

There are plenty of companies working in this space, including internet giant Google, which is also building an automated DR detection system. "There are a lot of companies and research groups following in our footsteps, which is exciting, because it shows that we're doing something valid and beneficial to patients," says Abramoff. (*See also "Eyenuk: Artificial Intelligence Boosts Diabetic Retinopathy Screening Rates,"* MedTech Strategist*, June 8, 2018.*)

On to the Next Challenge: An Autonomous AI Payment Model

Autonomous AI is something very new for the healthcare system, Abramoff says. "There are all these consequences of autonomous AI that were not anticipated, and we're forging a way through that, also, for the benefit of everyone else coming after us," he says.

According to IDx, its *IDx-DR* system is sold on a pay-per-click model: Providers bill insurers for the service, get reimbursed, and then share part of the reimbursement with IDx. But, currently, the technology relies on a payment code intended for more traditional ophthalmic imaging. Specifically, *IDx-DR* is using the existing CPT procedure code 92250 (fundus photography with interpretation and report). However, with the addition of a novel medical technology, autonomous AI, Abramoff—obviously not someone to shy away from a challenge—has been proposing an entirely new payment model for autonomous AI.

"I've been arguing for a while that we need a more general payment model for autonomous AI in healthcare. I've been working on that, and it's going faster than anticipated, which is exciting," says Abramoff.

This Just In: Congressional Briefing

On May 28, Abramoff participated in an IDx-sponsored Congressional briefing on Autonomous AI and Healthcare Savings. Other speakers at the event included Michael Hodgkins, MD, Chief Medical Information Officer at the Digital Health Office of the American Medical Association, and Liz Asai, co-founder and CEO of **3Derm Systems Inc.** 3Derm has developed a dermatological triage system that combines point-of-care autonomous AI and standardized imaging to diagnose skin lesions. These algorithms will be integrated with 3Derm's existing teledermatology triage system, which works with patients' existing networks of physicians to expedite dermatological care.

Hodgkins, Asai, and Abramoff discussed autonomous AI, including transparency and accountability for safety, efficacy and equity, as evaluated on the basis of scientific evidence by FDA. Panelists showed how currently, investments in autonomous AI R&D are held back by the twin risks of the FDA process and uncertainty about payments. They discussed ways to de-risk these investments, with the potential for immediate cost savings.

Specifically, Abramoff proposed a framework for clinical, workflow, and human factors validation, including machine learning design and training review, combined with preregistered clinical studies tied to patient outcome. All these elements must be accounted for before payment can be considered. The model requires accountability from the AI developer, and thus the medical liability lies primarily with the autonomous AI and not with the provider using it. It also includes a requirement for evidence of clinical usefulness, as measured by clinical adoption, and careful consideration of deployment by physicians.

POSITIVE SIGNS OUT OF CMS

But Many in Medtech Need to See More

>>David Filmore

Officials at the agency that oversees Medicare policy are certainly talking the talk in support of medtech innovation, and they are starting to walk the walk with new policies attempting to make improvements to the coverage, coding, and payment landscape for new devices. It is still early days though, and those in industry dealing with reimbursement challenges on the ground say a cultural shift at CMS is still needed.

Words and policies that have come out of the US Centers for Medicare and Medicaid Services in recent months are leading some in industry to a cautious optimism that CMS is turning a corner toward support for early adoption of medtech innovation. Meanwhile, many working in the trenches to win proper coverage, coding, and payment for new technologies remain skeptical, pointing to a need for a cultural shift and resource enhancement at the Medicare agency.

Device makers have increasingly experienced a more consistent path to achieving FDA approval and clearance, but firms are running into barriers on reimbursement. That has led to a widening gap of time between approval and the chance of achieving meaningful adoption, when companies are wading through a tangle of meetings, deadlines, and data requests from national CMS and/or local Medicare Administrative Contractors (MACs), not to mention the *American Medical Association CPT (Current Procedural Terminology) coding panel*.

SEEMA VERMA

But CMS under its current administrator, Seema Verma, has been sending out signals that it wants to forge a new way; Verma says that clearing the path for new technology to get a fair shake upon launch is one of her agency's top priorities. And officials in the White House have called for the need to improve the reimbursement process for medical devices, pointing specifically to the contributions the device sector makes to support the US economy.

"We're doing a lot of work on medical device stuff that nobody knows about, trying to figure out how America can maintain our dominance," Joe Grogan, who was serving as the top health official at the Office of Management and Budget and has since been elevated within the White House policy structure, said during a media briefing last fall.

More recently, words have been translated into some policy actions. Last October, CMS rolled out changes to its Medicare Program Integrity Manual in an attempt to add more clarity to the local coverage determination (LCD) process handled by MACs. A very small proportion of devices go before the national CMS office; a much larger number must be considered by the dozen or so MACs scattered around the country, either to establish LCDs or for claim-by-claim billing. But the LCD process is opaque, and each MAC tends to handle questions of evidence requirements, for instance, differently.

The recent reforms include changes such as requiring MACs to provide a standardized summary of clinical evidence supporting an LCD and ensuring that advisory committee meetings are open to the public. The updates are just being rolled out in practice, so it is too early to tell the impact, stakeholders say. In May, CMS issued an additional frequently-asked-questions document with the primary goal of making it clear to MACs that they can't automatically non-cover any technology just because it has a Category III CPT code (designated for emerging technologies, as opposed to Category I codes for more established services)–a barrier companies are often running up against.

In April, CMS came out with another proposal–this time relating to setting procedure payments–that seems to signal a shift in how the agency is viewing medical technology, to place more emphasis on value and less of a knee-jerk reaction to the front-end price tag. Specifically, the agency proposed reforms, as part of its annual hospital inpatient rulemaking process, to its

new-technology add-on payment (NTAP) program for hospital inpatient procedures (and related changes to a similar "pass through" program used for the outpatient setting).

For years, companies have complained that NTAP, intended to provide a temporary mechanism for paying for new technologies while Medicare figures out a longer-term policy, has been broken. They say it is too restrictive, allowing only a small handful of devices to qualify for the bonus payments. In addition, the size of the payment has often not been enough to bridge the gap between the technology's costs to hospitals and standard reimbursement rates. In this environment, hospitals are under increasing pressure to more critically assess which new technologies to adopt.

Now, CMS is proposing to improve the program by substantially lowering the barriers to a temporary NTAP for devices that are approved through FDA's Breakthrough Devices Program (they would qualify as long as the cost of the technology warrants it), while also increasing the bonus-payment cap for all qualifying devices. CMS is also considering reforms that could streamline the qualifying process for a broader set of technologies in the future. (*For more details on the program, see box "A New Take On New Tech?"*)

The recent policy proposals are very promising signs, industry advocates say.

"Under [CMS Administrator] Seema Verma's leadership, we have really seen the agency take a new direction related to innovation–very pro innovation, and wanting to make sure that new innovation is seen as a solution for helping Medicare patients in the future," Donald May, AdvaMed's executive VP for payment and healthcare delivery policy, said in a recent interview with *Market Pathways*.

"We are really pleased with this acknowledgement, that new innovation can both address improved quality for life for Medicare beneficiaries, and, in a lot of cases, lower cost overall."

What's Coming?

And CMS says there is a lot more coming.

"Our goal is to get new innovations to our beneficiaries concurrent with FDA approval by, one, removing government barriers to innovation, and two, harmonizing CMS coverage, coding, and payment processes," Verma said during a May 2 speech at the Medical Device Manufacturers Association (MDMA) annual meeting in Washington, DC.

Verma acknowledges that coverage, coding, and payment decisions are not always made in sequence. "This can lead to unpredictable pathways for innovators with respect to review timelines and engaging with CMS," she said at the MDMA meeting. Verma says her agency is working to enhance transparency and inter-agency coordination.

In addition, CMS wants to get itself more in sync with FDA processes. The two agencies have already been working together for years on the FDA-CMS Parallel Review Program, which provides a path for a simultaneous FDA approval and a proposed national coverage determination. That program has seen relatively limited use, but the agencies have also been working together informally with a greater number of individual companies to help bridge the gap between the regulatory and reimbursement processes.

The recent NTAP proposal is one example of an effort to sync up, as CMS will explicitly rely on FDA's determination that a device qualifies for "breakthrough" status to offer a bonus payment. Similarly, CMS relies on FDA's categorization of clinical trials (Category A for studies of experimental device types; Category B for more established device types) to inform its clinical trial coverage policies. Verma says she wants to further strengthen the ties, with an eye to coordinating reviews and minimizing redundancies.

There is also an implicit recognition by some at CMS that the Medicare agency is lacking in resources relative to FDA, so there are benefits to be gained from leveraging FDA's efforts as much as possible. Jeff Shuren, MD, the Director of the Center for Devices and Radiological Health (CDRH), and CMS Coverage and Analysis Group Director Tamara Syrek Jensen have previously discussed this issue and ways to help streamline the regulatory-to-reimbursement process.

Jensen, who spoke separately at the MDMA meeting, said that her office has been "working non-stop" on reforms related to medical innovation issues. "Hopefully there'll be a lot more ... over the next year," she said.

For one, Jensen's coverage office is working on a proposed rule that would provide automatic, transitional coverage to FDA breakthrough devices during a time period when the manufacturer would be required to collect data to support long-term coverage. That proposal, which the device industry has been working closely on with the agency, would very much parallel the NTAP inpatient rule concept for an automatic bonus payment for breakthrough devices.

"Because [CMS is] putting a structure for those technologies to be reimbursed with additional payments, both in the inpatient and outpatient systems, the coverage is somewhat implicit, unless the Coverage and Analysis Group or one of the local contractors actually make a decision to non-cover a technology," explained AdvaMed's May. "So, we believe we are most of the way there" with the NTAP proposal, he said.

But industry hopes the upcoming coverage proposal, which could be out in the coming months, will be a bit more expansive. Specifically, it wants CMS to include a provision that would allow a company to request that Medicare

temporarily cover any FDA approved or cleared device while the company commits to collecting addition data under CMS's established "coverage with evidence development" policy. Under industry's proposal, once the provisional period ends, coverage would continue until CMS or local MACs decide whether or not to establish specific coverage or non-coverage policies for the technology.

Skepticism Persists

For now, many industry executives and practitioners of reimbursement policy are taking a wait-and-see approach.

The tone coming out of CMS is promising. It is noteworthy, for instance, that in rolling out its fiscal year 2020 hospital inpatient prospective payment system rule, which ran almost 2,000 pages and addressed all the nitty-gritty facets of how hospitals are paid by Medicare to care for patients

A New Take On NEW TECH?

CMS unveiled its new-technology add-on payment (NTAP) reforms, as well as information on the latest NTAP candidates in the Medicare fiscal year 2020 hospital inpatient prospective payment system proposed rule that was released in April (*see Figure 1*). Although there have been some tweaks to the NTAP program since it was first established in 2001, these proposals would be the most significant changes to the program, which is intended provide a temporary bonus payment for new innovative technologies to support clinical adoption and sufficient clinical and cost data to support longer-term reimbursement policies.

The agency decided to address concerns with the NTAP program in three ways:

1 CMS proposes that any product designated by FDA as a "breakthrough device" will automatically qualify for an NTAP, as long the cost of the technology warrants it. That means, the manufacturer will not have to prove "substantial clinical improvement" over existing services or technologies. The bonus payment would last for two years, and the manufacturer would have to prove substantial clinical improvement after that time to gain an additional year of the payment. This would take effect beginning October 2020 (FY 2021) under the proposal.

2 Starting this October, the size of the NTAP bonus payment any qualifying device could receive would max out at 65% of the cost of the technology above the standard procedure rate, up from the 50% ceiling that has long been in place.

3 CMS is asking for input on a range of proposals to redefine what the term "substantial clinical improvement" means for the NTAP program. That threshold often stands in the way of a technology earning a payment.

FDA's breakthrough device program is reserved for products that FDA deems to address an unmet need for life-threatening or irreversibly debilitating conditions. It's a relatively selective program that requires FDA to commit extra resources to work with breakthrough sponsors on novel clinical trial designs, accelerated review, and other efforts.

That said, the program has been more active than originally anticipated, so the impact of granting bonus payments to this subset of devices is not trivial The agency has granted breakthrough designation to about 150 devices since the program started in 2015 and has approved at least 11 breakthrough devices so far. Examples of approved breakthrough devices include **Impulse Dynamics Inc.**'s *Optimizer Smart* implantable pulse generator for heart failure, **Pulmonx Corp.**'s *Zephyr* endobronchial valve and **IDx Technologies Inc.**'s *IDx-DR* autonomous artificial intelligence-based device for detecting diabetic retinopathy. (*see "IDx Technologies: AI Meets Market Access with a Breakthrough Diabetic Retinopathy Detection Device," this issue.*) The addition of an NTAP to the mix of incentives for breakthrough devices could drive increased interest by companies in the FDA breakthrough program.

Meanwhile, the increased payment ceiling would apply to any device accepted into NTAP, regardless of its breakthrough status. Device groups including AdvaMed previously have lobbied for increasing the ceiling up to 100% of the device cost. (Legislation introduced in the House last year would have set it at 80%.) But Don May, AdvaMed's reimbursement lead, says the

they admit, that the press release was headlined with the goal to "unleash medical innovation."

But companies say they continue to run up against a lot of barriers when dealing with CMS and MACs. Industry experts tell *Market Pathways* that some of the proposals filtering out so far will be relatively limited in reach, noting for instance that FDA's breakthrough program and the NTAP program may not be the right fit for many devices coming to market.

Efforts to improve MACs would be important but the impact of the recent LCD manual updates is still unclear. Early experiences suggest the changes might be making the LCD process even more formalized and structured than companies had bargained for.

"What's been interesting and frustrating for some companies, some clients, has been the formalization of all the processes, where they used to be

proposed 15% increase "is a significant change" that will be a "tremendous support for hospitals that will want to include new breakthrough and NTAP products in the services they offer their patients."

How important the payment increase will be to driving hospital adoption will likely be case-by-case. One device that would be immediately impacted if the proposal is finalized later this year would be **Boston Scientific Corp.**'s *Sentinel* cerebral protection system for transcatheter aortic valve replacement procedures.

The device qualified for an NTAP last year, allowing hospitals to collect an extra $1,400 for each procedure in which it is used. CMS wants to continue the NTAP in 2020 and with the elevated payment levels, *Sentinel* procedures would qualify for a $1,820 bonus. That could be useful, particularly with the recent FDA approval and US launch of Boston's *Lotus Edge* TAVR system, which the company will sell alongside the *Sentinel* device. Exactly what difference $420 will make is hard to say at this point. "We look forward to the final CMS ruling and the potential to reach more patients with our *Sentinel* technology" is all Boston Scientific spokeswoman Angela Mineo would say.

The third portion of the NTAP proposal could have very important longer-term implications but the specifics remain to be seen. CMS is considering a broad range of possible approaches to reposition what the "substantial clinical improvement" threshold means, with the goal of making it more transparent and reasonable for newly launched products. The agency is asking for open-ended comments from stakeholders on the best approach, in addition to floating specific ideas, including a proposal that substantial clinical improvement can be established simply by a device sponsor showing that a technology will be "broadly adopted among applicable providers and patients."

Public comments on the proposed rule are due to CMS by June 24. A final rule will be posted by late summer, to take effect October 1.

Figure 1

DEVICE NTAP CANDIDATES For FY 2020

» *Duragraft* vascular graft treatment*

Company: Somahlution

FDA Status: PMA approval anticipated July 2019

» *Eluvia* drug-eluting stent for peripheral artery disease

Company: Boston Scientific

FDA Status: PMA-approved September 2018

» *GammaTile* brachytherapy for brain tumors*

Company: GT Medical Technologies

FDA Status: 510(k)-cleared July 2018

» Supersaturated Oxygen (*SSO2*) Therapy for acute myocardial infarction patients*

Company: TherOx

FDA Status: PMA-approved April 2019

» *T2Bacteria* panel for sepsis-causing organisms

Company: T2 Biosystems

FDA Status: 510(k)-cleared May 2018

**Devices that have applied previously for NTAP but withdrew or were ineligible.*

Source: CMS

able to more informally interact with the MACs," said Louis Jacques, chief clinical officer for **ADVI Health LLC**, and a former CMS official. "And now they realize they *have* to go through a formal process. So sometimes you do get what you asked for."

Companies are still waiting to see if the recent frequently-asked-question guidance from CMS will cause a change in how MACs handle devices with Category III codes, and whether firms will be able to go back to the Medicare contractors to reconsider prior non-coverage determinations made purely because of the coding designation.

One of the biggest pain points for companies remains the process of securing a distinct billing code for a new technology, whether it is a HCPCS (Healthcare Common Procedure Coding System) code granted by CMS or a CPT code granted by the American Medical Association. At the May MDMA meeting, Administrator Verma announced one change intended to help give device-makers additional chances to qualify for a new HCPCS code that could support proper billing for a new technology. Specifically, CMS will be allowing semi-annual rather than annual opportunities to make a submission for a new code.

That is a helpful change, CMS watchers say, but many complications remain regarding the types of data and information that is being requested simply to support development of a new billing code.

Fundamentally, many industry concerns are more centered around the CMS' culture and its lack of resources, rather than specific regulations and policies. The knee-jerk sentiment of wanting to avoid paying for new technology with high price tags is still too powerful among agency staffers, several industry executives and reimbursement consultants told *Market Pathways*.

In addition, the basic procedural process with CMS is weighed down by ambiguity and lack of response.

In general, according to industry consultants who spoke to *Market Pathways*, responses from FDA, even when it is turning down a request from a company, are consistently signed by an individual and include a number to call with questions. Responses from CMS, meanwhile, may often come from a generic email address and do not include an individual to follow up with.

"I just want someone at CMS to read my clinical protocol," lamented one CEO of a venture-backed start-up with an FDA-cleared device seeking reimbursement.

Industry advocates who have been toiling for years with CMS and with Congress to improve things acknowledge the challenges, but they say the recent actions from the Medicare agency are positive first steps.

Once a clear-cut reimbursement route is established for breakthrough devices, for instance, the next step is to work on establishing solutions for other categories of medtech that don't have a straightforward path to take after gaining FDA approval or clearance, according to lobbyists working on the issue. There is also a recognition that CMS is under-resourced. Some have suggested an openness to the idea of industry user fees for CMS, in the mold of current FDA user fees, but that idea is far from being a full-fledged policy proposal.

Overall, the goal is to achieve a diversity of pathways that are each clear and predictable and relevant for different categories of services and technologies. It's worth keeping a watch in the coming months to see how these pathways are laid and where they go.

"WHAT'S BEEN INTERESTING AND FRUSTRATING FOR SOME COMPANIES, SOME CLIENTS, HAS BEEN THE FORMALIZATION OF ALL THE PROCESSES, WHERE THEY USED TO BE ABLE TO MORE INFORMALLY INTERACT WITH THE MACS."

—Louis Jacques,
Chief Clinical Officer
ADVI Health LLC

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EU MDR: Welcome to the New Reality

A panel of medtech CEOs and regulatory experts discuss what the future is likely to hold with the impending advent of the new European Medical Device Regulation. The key takeaway: be prepared for a major shift for everyone—large and small companies, new and existing products, European and US manufacturers and investors. There is no escaping the impact of MDR.

>>Stephen Levin

Medtech, as an industry broadly speaking, is highly compartmentalized across a range of parameters, among them different clinical or therapeutic categories, companies of varying sizes, global geographic variations, and an assorted range of functional responsibilities within organizations ranging from product companies to investors. As a result, new trends or changes in the rules governing one area may not have much impact on other spaces, siloed as they are. The impending new European Medical Device Regulation (MDR) stands as an exception to that pattern in that these new rules are poised to have a significant effect on a broad swath of the medtech landscape, extending well beyond European borders.

If there is one area of general consensus within the various sectors of the device industry, it is that life for many in the industry is likely to change significantly upon the effectuation of MDR, slated for next year. Perhaps the biggest misconception is that these new rules will only affect new products, leaving companies with devices currently on the market in Europe untouched. In fact, not only is that not true, but new products, far from possibly gaining increased attention under the new regimen, are likely to find themselves in the back of the queue as regulators and notified bodies attempt to recertify the 500,000+ devices already on the market so that clinicians can maintain the necessary level of continuity of care to avoid disrupting and diminishing the quality of patient outcomes.

Another misconception—one that continues to be fueled by the dilly-dallying accompanying the current Brexit debate—is that the European Commission will simply continue to kick this can down the road, rather than implement the new Regulation, maintaining the status quo. A large part of that view can be attributed to the fact that we have been hearing about this possible change in the European device regulatory process for nearly 30 years. Again, nothing could be further from the truth. Those who are alerting

the industry to the upcoming challenges of MDR should not be equated with Chicken Little—in this case, the sky will be darkening, if not falling. Incidents such as the PIP breast implant scandal, the metal-on-metal orthopedic problems, and the recent implant files articles highlighting medtech complications have not only fueled an attitude among many European regulators about the need to toughen the standards for bringing medical devices to market, but they have triggered additional debate about whether the MDR goes far enough.

These impending changes fly in the face of what had been a commonly used strategy by US start-ups of quickly getting CE mark to begin generating both clinical data and sales revenue to help support subsequent US commercialization. Occurring at a time when the US regulatory landscape is becoming more accountable and accessible for device companies through FDA programs like the breakthrough device pathway and the promotion of early feasibility studies, many companies and investors are now taking a second look at whether a Europe-first strategy makes sense given the shifts taking place in both regions. (*See "Managing Change in Global Medtech Regulation: A Tale of Two Systems" and "Jeff Shuren,10 Years in at CDRH," this issue.*)

With MDR right around the corner, the imminent new European regulatory climate was the topic of a widely attended panel at *MedTech Strategist*'s recent Dublin Innovation Summit, held in April. (*MedTech Strategist* is the publisher of this new publication.) The panel featured not only one of the pre-eminent experts on MDR, Serge Bernasconi, who heads MedTech Europe, the EU's medical device trade association, and has been on the frontlines of the MDR debate since its inception, but also a pair of experienced medtech CEOs, James Greene of **Medlumics SL** (miniaturizing OCT imaging technology to develop an RF ablation catheter to treat AF) and Jeffrey Jump of **MedAlliance SA** (drug-coated balloons), both of whom have had a longstanding interest in the potential impact of the new regulations on the operation of medtech companies, particularly start-ups. The panel was chaired by John Olden from Eugene F. Collins, one of Ireland's leading law firms with a strong presence in that country's well-established and growing medical device ecosystem. We publish this discussion here in the first issue of *MTS Market Pathways* based on both the relevance of the topic and the response generated at the conference, so that those not in attendance can benefit from this timely conversation. This discussion was edited for clarity and concision.

>>**John Olden**

>>**James Greene**

>>**Jeffrey Jump**

>>**Serge Bernasconi**

John Olden: Good afternoon. Just to explain briefly who you have here, first of all, my name is John Olden. I'm a partner with Eugene F. Collins. We've been delighted to have been associated with this conference every year since it started in 2013. We're an Irish law firm. We are based only in Ireland, work only with Irish companies or Irish transactions. But that said, we've worked with a great deal of the Irish companies that have been here over the years, including for example, Croivalve, Lucy O'Keefe's company. We've also acted with a lot of the venture capitalists who are here who have invested in Irish companies over the years. With me we have Serge Bernasconi of Medtech Europe; we have Jim Greene of MedLumics, and I know Jim going back to when he started here in Ireland some years ago with a different company; and Jeff Jump of MedAlliance. So guys, maybe to start, Jim and Jeff, given what has happened, it's interesting that the two of you each has a US background, you came from the US, but you came to Europe when you started out because that was the sensible thing to do. But you would not necessarily say that now? Today, to somebody who calls you from the US and says, "You've done it very well; should I do what you did and go to Europe? Would you agree?"

James Greene: I recommend that any company planning an EU-first clinical strategy should understand the uncertainty of the future MDR requirements, as they are significantly different from when we started in 2010 with Apica. We made a conscious decision, as many companies did, to base operations and live in Europe because we wanted to be really close to our customers. Basing

in Europe meant you were an hour away from being in clinic with your customer. This facilitates face-to-face interaction between engineers and clinicians throughout the entire product development process. As we'll talk about with the new MDR, depending on where you are in your development timeline, you'll fall under the new and uncertain CE mark requirements of the new MDR. In this case, it would be my recommendation that you look at the Early Feasibility Study (EFS) US pathway first. If you're in Europe, that means you will need to have a footprint in the US to execute on a US PMA pathway, but at least this is a more defined pathway that you can plan for.

Jeffrey Jump: I agree. I came to Europe in 1981 because I wanted to work on cool, new cardiovascular products, and the US environment at that time was not very welcoming, and the European environment, it was very predictable. You simply had to demonstrate things were safe, follow the recipe, and you could move very quickly. So that was very attractive. I think the reason that people should pay attention to the new MDR is this will be the single most disruptive factor facing our industry in Europe for at least the next ten years. It affects everyone—certainly it affects all these little companies with one product that we saw this week, but it also affects the most successful medical company in history, Medtronic, which has 80,000 products that it has to put through this MDR system. I don't know if everybody understands that. The MDR does not just apply to new, cool and innovative products. It applies to every single product in every single hospital or doctor's office in Europe today; they all have to go through this process, which is a huge thing.

JO: Just to explore that, Jeff, you were saying earlier today when we chatted about this, I mean this stretches down to literally the products that are already in use in hospitals, the products that are on shelves in general practitioners' surgeries, the products that are in pharmacies.

JJ: Exactly. And the problem is if you're somebody like Medtronic and you've got 80,000 products out there—there are over 500,000 products in Europe today. Daniel Shoukier wrote a book on this subject and he said 50% of those products are going to be gone. So you're going to go from 500,000 products to 250,000 products. He says 30% of medical device companies in Europe will be gone. And there will be deaths because of this process. There will be a physician who wants to use a specific product he or she has used before and it will not be available. This could be a life-threatening situation and they will not be able to use that product anymore because it didn't get accredited. You will read in your local newspaper about deaths as a result of this process. And that sounds quite dramatic, but I think we all agree that's a possible outcome of this whole scenario.

JO: Well, Serge, not to put you on the spot, but you're head of MedTech Europe, you've been aware of what's going on. In fairness to the people who came up with the idea, they would have looked and said, you know, the medical device directive goes back 28 years. Things have moved on; we need to move on. There was the PIP scandal. We need to improve upon this. Now maybe the pendulum swung too far, but when you listen to what Jeff says, what would you say—would you say it's the construct of the regulation is a problem? Or is it the implementation of it and what is around it? I mean for example, notified bodies are going to be critical, yet the number of notified bodies is going from sort of around 80 to around 50 or thereabouts, for Class 3 products.

Serge Bernasconi: Yes, this is a problem.

JO: Yeah. So without being sweeping about it, would you say this is a teething problem, or as Jim and Jeff have said, is this a more deep-rooted problem?

SB: First of all, hi, everyone, it's a pleasure to be back here. Just like to say one thing is that I think that I've participated in this a couple of times and I think I've said for quite a few times, let's be careful. This is going to cost a lot of money, take time, and most probably not everybody will survive this new regulation. Unfortunately, I have to agree with Jeff. I think that we're now basically in front of the wall, or getting closer and closer to the wall, if I can say this. Things are not that simple. I don't know if one would like to criticize the regulation by itself. I think that we knew from the very beginning that the new regulation that was going to be established for Europe would be much stronger, much more demanding than what was there before. That was a fact. As we worked with the Commission, the Parliament and the Council, we tried to obviously make sure that, as they were developing this new regulation, they took into consideration the way our industry operates. They did to some extent and also did not. The fact of the matter is this new regulation is much more demanding and does change tremendously the rules of how one will enter the EU market and how one will stay in the EU market. Now the regulation is what it is. We know it. The true challenge today is not so much the regulation per se. It's the transition between the old directive to the new regulation. We do have a significant challenge in front of us. We were able to maintain the notified body at the center of our system, and we avoided to go into EMA [European Medicines Agency] and a pharma-like system. But this required that all notified bodies in Europe would be redesignated to basically comply with the new regulation. We most probably underestimated how long that process was going to take. Out of the 58 notified bodies which are currently designated to certify product under the directive, today, we have only one which has been approved for certifying medical devices under the new regulation. [*Editor's Note: One more notified body has been designated since this discussion took place. See "EU Regulations Catch-Up: Where Things Stand One Year from Lift Off" in this issue.*]

JG: And that's BSI in the UK.

SB: That's just putting some pepper and salt on the issue. Yes, we do have one. I don't think it's a secret to anybody. It's BSI, which has been designated to give MDR certification. We have about 38 that have applied to the [European] Commission to become designated under MDR. The Commission continues to say that nobody should be worried about anything because things will be in place in due time. The problem is, what is due time? And we have a strong feeling that due time in the mind of the Commission is May 2020, which is when companies will have to switch over into the new regulation. Obviously, that's unacceptable to us because if that's the case, what Jeff predicted will definitely happen, that the vast majority of products which need to be re-certified will not be re-certified on time. Now the trick is it's not a question of whether or not the system will be ready. It's when the system will be ready. So that for the recertification part, which is potentially the biggest part that eventually the system has to handle up front, it will take time. It takes about three to nine months, I guess, for a product to be recertified. So you just have to do a little bit of math and then realize very quickly that we are already in a situation where we need the system to be operating. The Commission expects that 12 to 15 notified bodies should be designated by year-end 2019. That's their expectation. All this obviously is totally unacceptable to us. We've been trying to scream, shout, work with the commission to figure out solutions so that we can fix the problem. I cannot tell you, "don't worry, things are going to be fixed." We don't yet have solutions to this critical challenge.

JO: Can I ask you, sorry to interrupt you, but that's the recertification of existing products. But probably most of the people in the audience either have new products that they're hoping to bring to market or indeed they're investing in those companies. So where do they fit into that? And if a company is hoping—and I want to ask the guys in a while about their runway and stretching out a Series funding. But you know, if for a promoter or a company—no matter how good an entrepreneur you are, no matter how good your track record is, you're not Medtronic with tens of thousands of people and every notified body will say, "Well, Medtronic will be here in 40 years time, long after I've retired. I'm looking after Medtronic first".

SB: OK, let me try to give you a bit of a sense of the order in which things could occur. I think the number one priority is going to be given to actually what we call either Class 1, which will now require notified body certification, or up-classified products that basically went from a situation where they didn't need certification before, to now they're going to need it. So it's all Class 1, some of the Class 2's, and software, for example, that will now need certification. All of these are or should be the number one priority of the new system as these products cannot benefit to what's included in the regulation, which is a grace period for products that are Class 3 or implant types of products. Some of the class 2's also might benefit from the grace period. The grace period allows you to apply immediately for a product certification and/or re-certification using the medical device directive, not the regulation, and you will benefit from its validity, having to use the new regulation when then renewing the certificate or, at the latest, until 2024, whichever comes first. So, such a grace period, if you are eligible, will automatically give you more time to get into the new regulation. But that's really specific to Class 3 devices and implants.

Existing products can benefit from this if there is no significant change in the product. Now, let's talk about new products. Well, essentially you can imagine that new products come after all the ones I just mentioned. Because the priority is to make sure that whatever is on the market today stays on the market. That's the priority. And then the new products will come next. Then the decision for the new products will be: do I go for a certification under the old directive or do I try to go already into the new regulation? One of the critical issues is to find today a notified body that will accept a new file – I'm saying a new file—from

"THE DECISION FOR THE NEW PRODUCTS WILL BE: DO I GO FOR A CERTIFICATION UNDER THE OLD DIRECTIVE OR DO I TRY TO GO ALREADY INTO THE NEW REGULATION? ONE OF THE CRITICAL ISSUES IS TO FIND TODAY A NOTIFIED BODY THAT WILL ACCEPT A NEW FILE – I'M SAYING A NEW FILE—FROM A RELATIVELY NEW DESIGNATION, WHICH FRANKLY MOST OF THEM HAVE FAILED TO OBTAIN."

—Serge Bernasconi

> "I WOULD CAUTION EVERYBODY. PUT A GOOD MEASURE OF CONTINGENCY PLANNING INTO YOUR TIMELINE AND FINANCING IF YOU INTEND TO GO FOR A CE MARK-FIRST STRATEGY.
>
> —**James Greene**

a relatively new company trying to obtain a certification. These guys are right now up to here with the old products, and they are very focused in trying to obtain their designation, which frankly most of them have failed to obtain. They've been rejected by the commission and the member states. So they basically have to respond to their audit points to be able to obtain their designation.

JO: OK, thank you. So Jeff, I know you don't have VC money at the moment in some of the companies you're working with, but Jim, you do. Could you talk about MDR in your planning for the Series B for MedLumics, what did that mean? When everybody drilled down beyond the term sheet and said, "This is the time line, this is where the money is going to be spent". How did all of that work out?

JG: Sure. When we raised and invested in the Series B round [March 2017], we were still considering CE mark first. When we initially started working with the notified body, which is the one that's certified, we started from a study size of 60 patients. And then as we moved through our development plan it became very obvious that we were not going to fit into the MDD [Medical Device Directive—the existing regulatory program pre-MDR] as we would not be able to supply our clinical data fully before October of 2019, which is their cut off point for accepting any new filings. Requirements also became very uncertain in terms of how many patients will be required, what kind of evidence will be required. We know now that we're not going to really be able to base it on a predicate device in terms of the technical file, because we're not going to have access to that technical file from our competitors, obviously. So the numbers of patients could be, we were informed, anywhere from 150 to maybe 400 patients for a Class 3 RF ablation catheter, which has an optical component to it, and we no longer can base the regulatory pathway on predicate devices in the market. So what happens then? Now you look at the milestone timeline that you financed to as compared to the new MDR requirements and all of a sudden your timeline for CE mark approval is so severely extended that you need an additional Power Point slide to capture this delay to commercial approval. In response, we transitioned to go to the US to start to negotiate for an early feasibility study plan, which is now a faster route to FIH [first in human] clinical application. Funny—it's kind of like the old is new again. What we're experiencing now in Europe was kind of the old FDA, and now the new FDA is super collaborative - conversations back and forth on how we can reach FIH study, and what data we need to deliver along a very specific and predictable timeline. It may not be the number that you like, but it's a predictable number that we can fund. So I would caution everybody. Put a good measure of contingency planning into your timeline and financing if you intend to go for a CE mark-first strategy.

JO: And Jeff, that leads into use or the non-permitted use in future of equivalency. Can you comment on how you think that's going to impact medtech companies?

JJ: Adding to what Jim said, I think this whole uncertainty thing, which used to be the hallmark of what we had in Europe—we had certainty. We knew we had a recipe to follow, we knew when we would start, we knew when we would get out. This MDR has introduced a whole area of uncertainty, and quite frankly, if you haven't started through the old system, the MDD, now it's too late. You can't get it through the system, so you have to do the new MDR system. And as Jim was saying, that means in the past you can go against—I have to pick a company that's not here—Boston. You have a product that you think is better than the existing Boston product. You used to be able to use their clinical data, demonstrate whatever you thought in your product was a little bit better, and then you could get approval. Well, now you can no longer do this because you have to get all the bench data, all the preclinical data. And so you have to go to Boston and say, I think I have a product that's a little bit better than yours. I would like to compete with you. Do you mind giving me all your preclinical and bench data so I can get approval? Good luck with that. So no, I think like Jim said, if you haven't gone through the MDD process now, it's almost impossible to get a notified body's attention because they're trying to get accredited. We only have one notified body accredited for MDR and it's British. You have to look at markets outside Europe, I'm afraid, with new products for the next five, maybe 10 years until this settles. It will settle, but there's going to be huge disruption in the meantime.

And there are additional things like they added the requirement to go through a panel. As Jim was saying, they kind of

copied the FDA. The reason Jim and I came here was because the FDA wasn't working so well. They realized this 30 years later and have now changed the FDA because they realized they were ten years behind. When people like Steve Jobs had to come to Europe to receive the latest treatment, people started to realize. So they changed their system, but then in Europe, we adopted the idea of creating a panel. A panel for the FDA is just a recommendation. But the panel in the MDR is binding. If the panel isn't brave and honest enough to say your project should go to a notified body, you cannot take it to the notified body. And the panel is supposed to be a panel of experts, but the only criteria that they've given is that they can't have any affiliation with industry. So if you're an expert on mitral valves, for example, how do you become an expert on mitral valve if you have no affiliation with industry? It's going to be difficult, and there are going to be different interpretations by different notified bodies of the same MDR regulations.

JO: And Serge, not to suggest that you're defending MDR or how it came to be what it is, do you have any observations on how the new rules on equivalence came to be what they are? Like what led to that process. I mean, if I understood it the way Jeff put it, previously you can look at publicly verified information and say, "We're working off that, and this is where we differ". But you can't do that now because you can't rely on that kind of information.

SB: I think that, at the end of the day, what led to this whole process is probably exactly what Jeff said: it had gotten so predictable in Europe, and one shouldn't say easy because that would be the wrong word to use. I would say there was a pretty straightforward recipe in how you could get a product approved through the CE marking. And we can also say, I think, the process was taken advantage of. I'm sorry to have to say this.

So on one side you had a system which was taken advantage of and potentially products with very limited data got to the market. We got our set of scandals and different problems that got into the way. And it is not only scandals coming from the PIP [breast implants] situation that everybody knows because that one, everybody would have a tendency to agree that it's fraud, but also the other scandals with medical devices. I think when you put all this together you get to a situation where the politicians in Brussels said enough is enough. You guys have enjoyed your life for a while. We're going now to get this back to order.

Now on top of that, in the recent months, we have had interesting coverage by journalists of the industry, not only in Europe but also in the US, but more heavily in Europe. It's interesting to analyze the reactions to that. We did not get much of a reaction from patients in Europe. We actually got reactions from regulators saying essentially two things: the new regulation has been designed to respond to these questions, but it might not be enough. They actually want more. Now nobody really wants to know or try to define what is more. But what we could understand is they continuously go back to the fact that there are no reasons why medical devices should not be treated as pharma. They should be basically treated exactly the same way. This puts pressure on the system and we have to be careful about what we do because we don't want to go back to a discussion trying to reinvent a new regulation and we need to be focused on transitioning into what has been voted for.

So I'm sorry to say, yes, the situation is challenging at this point in time. We are working to try to get solutions. We might not get solutions for everyone; let's face it, I would be lying to you if I would say we will, but we will continue to try hard. I think we owe that kind of transparency to all of you. And I agree with what Jeff said: in the next few years, Europe might not be the most attractive place when you have a new product you want to put on the market, as it once used to be. However, it remains a very attractive environment for the ideas that lead to new products. I think that in Europe we have the capacity to invent, develop, and create fantastic innovation. That we can do still in Europe. Then after that, the next step of going to market, unfortunately, whether you are developing an idea or if you are investors, Europe is not going to be as attractive as it used to be for the next few years.

JG: It's a shame, but it's true.

SB: If I'm an investor, I have to be extremely careful because I have to make sure that the people I'm working with have highly anticipated the impact of this new regulation. And that this new regulation is most probably going to cost more in terms of development, and it will take more time. So the return that one would be looking for now is very different than what it used to look like before.

JO: I'm trying to keep some sense of optimism. There are a lot of people in Europe. There are a lot of people involved in medtech. They're here. And the FDA—you can do some of the clinical trialing for FDA purposes in Europe now, am I right?

JJ: Absolutely.

JO: Is there any bright spot on the horizon? And I ask because everybody knows the VC model: the 10-year fund, five years to invest and five years to reap. Even if somebody's launched today, are we saying that the next two or three years in Europe are not going to be good? I know for the VCs very often the funds of funds are saying to them, "Where are your shovel ready investments?" So MDR being what it is, are there any bright spots?

JJ: I'm the big naysayer, but there are some bright spots. There are some good things for patients in the MDR, there are

> "I THINK THE FIRST GROUP WHO CAN HELP US BEFORE THE PATIENTS ARE THE DOCTORS. I DON'T THINK THE DOCTORS REALIZE THAT THIS IS HAPPENING."
>
> —**Jeffrey Jump**

some good things in data transparency and data collection I think are good. It's bad that the MDR has no provision for innovation. That could lead to the inverse of what happened with the FDA where now you can get a breakthrough status, where the FDA is accepting 30 to 50% of the patients from Europe. So ironically, you'll be able to do FDA studies in Europe before you can get European approval. It's kind of flipped everything on its head.

JO: Just drill down, Jeff, if you wouldn't mind to the granularity of that, doing some of those trials in Europe. What would be the value of that in the European context, in the MDR context?

JJ: Well, I don't know if it's value from the MDR, but it keeps all the engineers and ideas. I mean we've been enjoying the 40 years of glory with European innovation. I mean most of the products in the US and in China came out of Europe in the last 40 years. So those people are still here. I guess what we're saying is you just might seek out other markets, just like you used to from the US, come to Europe first. You can still develop innovative products here, but this may not be the first market they go to.

JO: Right.

JG: I think it'll also bring forward this idea we've discussed for a number of years about harmonization of different regulatory systems. We always talk about this picture of being able to have both a mixture of European and US patients in the same study. It'll require work upfront to negotiate early with the FDA and also with our European partners to make that a reality. But if we can do that, it'll prevent us from having to exclude one group versus the other. And I think the innovation that we have here, along with innovation in the US blended together is going to make a much more powerful clinical outcome, which should result in better products that we can bring to a larger geographic market. So it will require work, but I think it's actually forcing something that needs to happen.

JO: And what do you think it'll mean for the very young companies that are starting up. Has the game just gotten very, very expensive now? So that even in your first round of financing you have to raise more money—and somebody touched on the following point this morning, namely the difficulty of trying to value the first round, which is why many investors are going in for convertible loan notes on a first round and pricing them at a discount to the subsequent Series A round it seems.

JJ: One other part of the MDR is that you have to have an authorized representative and you have to have a regulatory expert within your company. So if you're a small company with six or seven engineers, more than 10% of your work population has got to be a regulatory person. Whereas before, you could rent those. And if you can't compare directly, as with the 510(k) process, then you have a lot longer preclinical bench period that you have to finance, and also you have the complication that it's harder to get into clinical cases. So it's basically just going to take longer and cost more. And companies need to plan for it, and investors need to plan for it, and you need to play smart. Go where it makes sense.

JO: OK, that's fair.

SB: I think we owe it to the audience to be as realistic as possible. I don't want to tell you don't worry, everything will be fine. Obviously, we're going to try to fix as many of these issues as we can. I think it's good to be very realistic, above all when you are a small company and you are looking to the future, or when you are an investor. Right now, yes, Europe, despite its great overall potential, for the next few years, position it as an uncertain environment where predictability is quite hard to get. That has to be taken into consideration.

JJ: It will get sorted out, but there probably is going to be a crisis. There's going to be some bad things that happen that cause politicians to react, like last time. I mean last time, the breast implant scandal, that was fraud. That had nothing to do with following regulations. That was against the law. But yet it inspired this whole spiral where we ended up with what we have today.

SB: And we cannot ignore the Brexit issue on top of it. That's just the cherry on the cake.

JO: Given that there's only one approval body, which is in the UK.

SB: It's a pretty big cherry because a lot of companies have established themselves in the UK or been using that notified body.

JJ: Forty percent of medical products are approved through UK notified

bodies. And after Friday that might not be possible. [*Editor's Note: That was the day on which the UK was scheduled to leave the EU, but, subsequently, the Brexit date was delayed until October 31.*] I mean I know of one company that's been working with a UK notified body for three years, and the notified body said that they were going to Amsterdam, and that was how they were going to get around the whole Brexit problem. They got audited by the Dutch authority and guess what? They didn't pass because they didn't have a significant amount of people there or resources there. But for whatever reason, they didn't pass, so they had to tell this company two weeks ago that "We can't give you CE mark unless we can get it done in the next week. So you're going to have to go to a different notified body." And going to a notified body in Europe, those 57 that are left, it's really difficult to get their attention, particularly if you only have one product and you're not trying to re-establish products that already have CE mark approval.

JO: Jim, do you have anything that you wanted to say to wrap things up?

JG: In regard to funding new ventures, I believe investors and innovators will assess innovative technology in much the same way—is it truly breakthrough and addressing a big enough clinical need that will attract strategics to generate large multiples at exit. The key question is how much time and cost the MDR will add to the venture that will deplete the size of the multiple at exit. In short, is it going to be worth it for our investors to come on board? Understanding this entry point in light of the MDR will be important to entrepreneurs in laying out their funding strategy, including non-dilutive funding, and how it will impact investors to minimize risk for VC investment and initial dilution for the company.

Audience Question: Has there been a reaction to the new regulation from European consumers who, as prospective patients, run the risk of not being able to receive the best medical care and technology? Not everyone can fly to the US or elsewhere to receive the necessary treatment.

JO: They might only have to fly to the UK.

SB: Maybe the UK is the way out. I think that the interesting difference between the US and Europe is that the health systems are structured differently. For that reason, the recent coverage by journalists on the whole issue of medical devices did not get picked up as much by patients in Europe. And there is a simple reason for that, which is very different in the US. In Europe the patient often doesn't pay. The patient is covered by a social system. So the implication of the patient vis-à-vis devices is totally different than the implication it could have in the US. Now the ones who picked up on this issue in Europe, however, were the regulators in each country. And the countries basically now went back and said, Gee, it's true, this is not right, and now we are seeing registries established in Germany and I think in Italy, Spain, and France looking into these issues. So now you have all the countries trying to react and saying what we have in the new regulation is not enough; we will want more. Now, should patients react? We believe they should, yes. We need to make the patient much more aware of the situation because they're going to potentially suffer at a point in time from the situation. Unfortunately, in Europe, broadly speaking, access to patients is not very well structured. It's quite well structured at the country level, but not at the European level.

JJ: I think the first group who can help us before the patients are the doctors. I don't think the doctors realize that this is happening, that perhaps one device that they use two or three times a year to save a patient's life, and they've depended on for 30 years, and they go to find it and it won't be there, and they have to explain to the family what happened, that's when it's going to become real for people, I think. So the doctors really can be our main advocate, I think, once we try to change this. I believe it will get sorted out eventually, but it's going to be a mess for a while.

SB: You could very well be in trouble if you're going for surgery on the first of June 2020, because surgeons may not have any scalpels with which to perform the surgery.

JJ: Every product, every single product has to get recertified.

JO: All right. Gentlemen, thank you very much.

FDA OUTPUT

Novel Device Approvals, Breakthrough Designations, Class I Recalls, and Warning Letters

Novel Device Approvals

5/31/19
»TransMedics
Device: Organ Care System Lung System
Approval #: P160013
Type: Panel-Track PMA Supplement

5/24/19
» QIAGEN
Device: therascreen PIK3CA RGQ PCR Kit
Approval #: P190001
Type: Original PMA

5/24/19
» QIAGEN
Device: therascreen PIK3CA PLASMA RGQ PCR Kit
Approval #: P190004
Type: Original PMA

5/23/19
»CD Diagnostics
Device: Synovasure Alpha Defensin Lateral Flow Test Kits
Approval #: DEN180032
Type: De Novo

5/23/19
»InBios International
Device: ZIKV Detect 2.0 IgM Capture ELISA
Approval #: DEN180069
Type: De Novo

5/20/19
»Theranica Bioelectronics
Device: Nerivio Migra
Approval #: DEN180059
Type: De Novo

5/16/19
»Stryker Neurovascular
Device: Neuroform Atlas Stent System
Approval #: P180031
Type: Original PMA

5/2/19
»Boston Scientific
Device: VICI VENOUS STENT System
Approval #: P180013
Type: Original PMA

Breakthrough Designations

5/30/19
»Resolution Bioscience
Device: Resolution HRD liquid biopsy assay
Target: Oncology companion diagnostic

5/30/19
»CancerSEEK
Device: Thrive
Target: Oncology diagnostic

5/23/19
»Amprion
Device: Protein Misfolding Cyclic Amplification
Target: Parkinson's disease

5/15/19
»BioPorto
Device: NGAL Test
Target: Acute kidney injury

5/13/19
»Grail
Device: Multi-cancer early detection test
Target: Early cancer detection

5/8/19
»Optina Diagnostics
Device: Optina retinal imaging platform
Target: Alzheimer's disease/ Dementia

5/8/19
»FARAPULSE
Device: Endocardial Ablation System
Target: Atrial fibrillation

5/6/19
»Natera
Device: Signatera test
Target: Oncology diagnostics

5/3/19
»Caris Life Sciences
Device: MI Transcriptome companion diagnostic test
Target: Oncology diagnostics

5/2/19
»Renalytix
Device: KidneyIntelX
Target: Kidney disease diagnosis

5/2/19
»Concept Medical
Device: MagicTouch
Target: Coronary in-stent restenosis

Class 1 Recalls

5/28/19

»Terumo

Device: Portico Solo Re-Collapsible Access System, Model #s PRTSOLO-19 & 20

Recall #: Z-1376-2019

5/28/19

»Terumo

Device: SOLOPATH Balloon Expandable Trans-Femoral System, Model #s STFI-1425-2135

Recall #: Z-1374-2019

5/28/19

»Terumo

Device: SOLOPATH Re-Collapsible Access System, Model Numbers SR-1925-SR2435

Recall #: Z-1375-2019

5/23/19

»Beckman Coulter

Device: UniCel DxH 600-900 Coulter Cellular Analysis Systems

Recall #: Z-1382-2019 – Z-1384-2019

5/21/19

»Edwards Lifescience

Device: EV1000 Clinical Platform, Models: EV1000A, EV1000NI, EV1000CS

Recall #: Z-1193-2019

5/20/19

»Integra LifeSciences

Device: LimiTorr External CSF Drainage and Monitoring Systems

Recall #: Z-1312-2019

5/20/19

»Integra LifeSciences

Device: MoniTorr ICP External CSF Drainage and Monitoring Systems

Recall #: Z-1310-2019

5/20/19

»Integra LifeSciences

Device: MoniTorr INS1100 INS-1100 CSF Drainage System used with Pole Mount System

Recall #: Z-1311-2019

5/15/19

»Ethicon Endo-Surgery

Device: Intraluminal Staplers, various models and sizes

Recall #: Z-1268-2019 -Z-1278-2019

5/6/19

»Alpha Omega Engineering

Device: Neuro Omega System, incorporating HaGuide software for neurological and neurosurgical use

Recall #: Z-1216-2019

Warning Letters

5/13/19

»Orchid Orthopedic Solutions

Citations: Quality System Regulation (QSR)

Issuing Office: Center for Devices and Radiological Health

5/9/19

»Zeller Power Products

Citations: QSR; Unique Device Identification; Registration and Listing

Issuing Office: Div. of Medical Device and Radiological Health Operations West

5/9/19

»Rechargeable Power Energy North America

Citations: QSR; Medical Device Reporting; Registration and Listing

Issuing Office: Division of Medical Device and Radiological Health Operations West (MDRHW)

HEATHER ROSECRANS

FOUR TIPS for Working with Your FDA Reviewer

>>David Filmore

Device companies need to understand the mindset of device reviewers when they are assigned a new submission, says long-time FDAer and 510(k) expert Heather Rosecrans. Here, she provides some helpful tips for firms to effectively work with a reviewer to get a submission through FDA's process.

"It can be a little scary to be a reviewer," says FDA device-center veteran Heather Rosecrans.

"When you're a reviewer, those devices become your devices," Rosecrans said during a panel discussion at the Food and Drug Law Institute annual meeting in Washington DC in May. "You never want to see them appear in the newspaper for anything wrong; you never want to do anything wrong."

Rosecrans has a pretty good set of experiences on which to base her characterization. She spent more than 30 years at FDA's device center, including almost two decades overseeing the 510(k) program. She now works with companies on FDA issues as EVP of Medical Devices and Combination Products at Greenleaf Health and as VP of Regulatory Affairs at the Medical Device Manufacturers Association. During the FDLI panel, she took a few minutes to provide a reviewer's "bottom-up" view of the review process for industry folks attending the meeting.

"When you're working with the reviewer, you really want to know who your audience is, who you're working with," Rosecrans said. FDA device reviewers are extremely dedicated to the job of clearing and approving safe and effective devices in a "fair and balanced way," but they are often worried something will be missed. Its best for the device sponsor, particularly for 510(k) submissions, to see its primary role as a support and guide for the reviewer throughout process, Rosecrans suggested. See box for four key takeaways from her remarks.

1 Sliced bread will do.

One thing Rosecrans recommends against is to go to FDA and say "this is going to change the practice of medicine, or this is the best thing you've ever seen. That's what you say when you go to the patent office," she noted. "But when you come to FDA you might not want to say that," unless you're in the Breakthrough Device Program.

She suggested that the newer and more innovative a device is perceived to be, the more skeptical the reviewer may be. That could add pressure to dig deeper and ask more questions.

2 Make haste, let them cut and paste.

Companies should go into the review process knowing the contents of their submissions backwards and forwards and be ready to explain it to the reviewer in detail. Sponsors should be aware that their reviewer may not have been able to read the product-relevant FDA guidance documents in the same depth as the company because she needs to be familiar with a broader range of FDA products and guidelines.

"You have to tell your story really well," Rosecrans noted. "You have to have an excellent device description, and you can go [into] detail with clinical processes, exactly how it is to be used. Don't be afraid to do that.

"Don't expect that they totally understand the situation—spoon-feed it to them. Put it all out in a way that they can just cut and paste it into their review memo. You can do that. I think they're happy to plagiarize."

3 Please push back.

The lead reviewer, who is often an engineer, will typically send a submission for consults with other agency experts, including sterility experts and physician medical officers, she explains. The consults may come back with deficiency observations that the reviewer and branch chief may not fully understand. "The reviewer can't tell the medical officer exactly how to change that deficiency," Rosecrans said.

"They're relying on you to push back, particularly for innovative devices. Come in and have a submission issue meeting … and explain it to them."

4 Don't forget FOIA.

Once the review process is complete, one step companies should always take, Rosecrans notes, is to submit a Freedom of Information Act (FOIA) request "for all the reviewers' memos, every single reviewer in that file." The goal, she explains, is to "know what's going on behind the scenes so you can be better prepared next time."

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Fogarty Institute for Innovation

STEPHEN LEVIN,
CO-EDITOR-IN-CHIEF

Managing Change in Global Medtech Regulation:

A Tale of Two Systems

US and European regulators are moving in opposite directions. How should the medical device industry cope?

In psychology, cognitive dissonance results from trying to maintain contradictory beliefs or positions simultaneously because humans prefer internal consistency. Welcome to the current state of global medical device regulation, particularly in the US and Europe. I recently attended two US medtech conferences and both featured sessions on international medical device regulation harmonization, a topic that has been under discussion for years. Yet, at the same time, we are seeing perhaps the clearest divide ever between the US and Europe since Pangaea split, with their respective regulatory regimens rapidly moving in opposite directions. And all signs point to that gulf continuing to grow with the implementation of the new European Medical Device Regulation (MDR), scheduled for May of 2020.

All of this is taking place in an industry that, while still US-centered, is becoming increasingly globalized, albeit at a time when the concept of globalization has progressively fallen out of favor on the worldwide political stage. Since industry as a whole prefers consistency and predictability, will these changes impact only certain medtech sectors or have a broader effect, and if it's the latter, how will medtech respond to these potentially tectonic shifts?

While we have seen significant changes in device regulatory climates before—one need look back no further than the FDA in the 1990s—the consensus view is that the shift about to occur as the result of MDR will be on a larger scale than seen previously. That is largely due to the fact that, like it or not, medtech is more globally inter-connected than ever before. And for that reason, the impact of these changes will be felt across nearly all elements of the device industry—product companies and investors large and small, US and European, in all clinical categories—with the biggest burden being the additional clinical data required and the time and resources required to collect it. Regulatory, financing, and commercialization timelines will all need to be adjusted to account for these impending changes.

Further, there is a common misconception that new products will be hardest hit, when in fact the biggest challenge will be in re-certifying the 500,000+ devices currently on the market with the limited number of notified bodies that are currently approved (two, as I write this). Indeed, new products are likely to face increased delays as they take their place in the back of the regulatory queue behind current products that clinicians depend on to perform procedures and deliver care, lest regulators risk triggering a healthcare delivery crisis across Europe. But start-ups with innovative technologies won't be the only ones hit. Large companies face the tough decisions of figuring out which of their existing products justify the added cost to produce required new clinical data. That process is likely to spur a large-scale trimming of product lines through wholesale rounds of pipeline management.

The biggest shift resulting from MDR is likely to be a turnabout in strategy on the part of medtech companies, primarily those in the US. Rather than looking to Europe to get quick CE mark approval to begin generating early revenue and clinical data to support entry into the US market—as has been the increased practice of many emerging players—we are likely to see companies, especially those already based in the US, focus on their domestic market first. That strategy shift is made easier by the concomitant changes that have been taking place at FDA. For while the European regulatory landscape is getting more challenging, the FDA is becoming more predictable, accountable, and generally easier for companies to work with through programs like the breakthrough device plan and promotion of early feasibility studies. That US-first strategy, obviously, won't be a viable option for all emerging companies; European-based start-ups will largely have to ride out the transition to MDR by provisioning for this new reality. But US companies are likely to put Europe on the back burner until there is greater clarity as to how to operate under the new regimen.

Does this mean that any notion of global harmonization in medtech remains merely a pipedream? Actually, no; the future is not as gloomy as it might appear. Progress is being made in areas like the Medical Device Single Audit Program (which involves the US, Canada, Brazil, Japan, and Australia), FDA's ongoing alignment with ISO 13485 standards, and in the use of unique device identifiers (UDIs). Small steps, admittedly, but progress nonetheless. Also, on a different geographic front, I am hearing anecdotally about companies that have been successfully able to use US and European clinical data to achieve regulatory approvals in Japan, no small accomplishment given how challenging it has been for non-Japanese companies to crack that market over the years.

So as US and European regulators continue to move in opposite directions, how should the medtech industry deal with these looming changes? F. Scott Fitzgerald's words could prove helpful: "The test of a first-rate intelligence is the ability to hold two opposed ideas in mind at the same time and still retain the ability to function."

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