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Micro-Invasive Glaucoma Implants Mark Hottest Growth Spot In Eye Surgery Products Market

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Cataracts, the leading cause of blindness, affect some 120 million people worldwide, but only an estimated 15% of people with cataracts are being treated with cataract removal surgery, which provides a huge window of opportunity for device makers to address this unmet need.

While some 20 million cataract surgeries of all types are performed each year worldwide, most procedures are done in developed nations. But even in developed nations, such as the US and Europe, only a certain percentage of people are being treated with today's sophisticated phacoemulsification systems or ultrasound "phaco" systems to remove cataracts and then replace it with an artificial intraocular lens (IOL); which is another hot area for device makers developing premium IOLs that address vision problems like astigmatism and potentially eliminates the need for prescription glasses. But with greater access to care and improved income, device makers will find potentially lucrative opportunities in emerging markets such as India, Asia and Latin America, areas with strong demand due to underpenetration of next-generation surgical techniques and the dire need to prevent blindness in a large and growing population.

The incidence of glaucoma, the second-leading cause of blindness, is expected to rise to 76 million by 2020 and 112 million people by 2040 worldwide and disproportionally affects people in Asia and Africa due to a lack of diagnosis and care.

Early treatment for glaucoma is critical for preventing vision loss. The first line of treatment is typically eye drops, which has shown to cut the risk of developing glaucoma by about half, but these medications are also very costly, burdensome or hard to administer and have shown serious compliance issues. Surgical treatments to address the abnormally elevated intraocular pressure (IOP) caused by inadequate draining of the trabecular network, can involve laser surgery, conventional open surgery or a combination of the two. But emerging micro-invasive glaucoma surgery (MIGS) devices, which are tiny drainage implants, are seen as filling an important gap in the treatment of glaucoma, and while promising, require much more thorough investigation.

CONTINUED ON PAGE 17

FROM THE EDITORS OF: **THE GRAY SHEET, CLINICA, START-UP** AND **MEDTECH INSIGHT NEWSLETTER**

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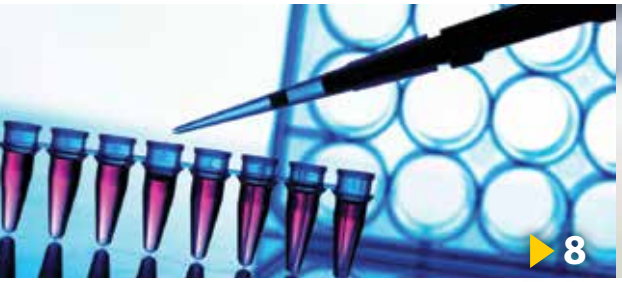
8


13


16

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US POLICY & REGULATION

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Exec Chat: Johnson & Johnson Brings Together Physician Education Programs In The J&J Institute

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Johnson & Johnson recently launched the Johnson & Johnson Institute to bring together its diverse collection of physician training programs into one system that can meet physicians' training needs, almost anywhere at any time.

"The J&J Institute combines comprehensive global educational programs to harness the size, reach, resources and collective passion of Johnson & Johnson Family of Companies to enhance human health," the company said Nov. 2. The J&J Institute staff train clinicians around the world on a wide variety of clinical procedures with the latest training technology, including virtual reality simulations, as well as online and mobile training technology.

Diana Bacci-Walsh, the Vice President of North American Education Solutions for Johnson & Johnson Medical Devices, oversees the day-to-day operations of the Johnson & Johnson Institute in North America. In her role, she leads the Center of Excellence that includes Professional Education, Sales Training and Development, Stakeholder Engagement, Digital Education, and Clinical Simulation, and oversees strategic initiatives for J&J's Cardiovascular and Specialty Solutions, DePuy Synthes, and Ethicon businesses. She works with sales, marketing and strategic account teams to build education programs across North America.

Bacci-Walsh also supports product launches with new education programs and maintains partnerships with medical professional societies. And she is a member of J&J's North America Regional Leadership Team and the Academic Orthopedic Consortium, an organization of academic orthopedic departments.

Diana Bacci-Walsh, VP-North America Education Solutions, Johnson & Johnson Medical Devices

Bacci-Walsh talked to Medtech Insight about the new Institute and how it fits into Johnson & Johnson's corporate-wide effort to adapt to the emerging value-based care environment.

Medtech Insight: What is the need that the J&J Institute intended to fill and how will it do that?

Diana Bacci-Walsh: Essentially, we've come together now with 26 institutes across the globe. Historically, however, we had one [center for each specialty] - one focused perhaps on orthopedics in one geography, and then in another geography we focused on general surgery or electrophysiology. We weren't available to our customers in a way that we wanted to be, but we want to be that preferred partner in education for our customers such that we could give them the right education at the right time.

What we've done is come together and created these J&J Institutes such that, for example, if a surgeon needs training and wants to do a particular surgical procedure in the upcoming months, and may not be as familiar with our instrumentation or with a particular procedure, we can really customize the education and be available for that physician when he needs the training.

We're really excited about this, because it not only allows us to really customize curricula, but it also allows us to take a more holistic approach to education.

For example, an orthopedic surgeon comes to one of our institutes and joins us for a total knee replacement course. We can ask that surgeon if he wants to invite his OR team as well. More and more we're taking a team approach towards education, so he may want to invite his scrub tech or his PA. And what we can do is look at the procedure in total.

For example, when they make that initial cut in a surgery, we have products that help with blood management. While the surgeon may be focusing on the knee replacement, the PA can be thinking about what sutures he or she is going to use to close the incision. We can now take this more holistic approach because we have such depth and breadth of product.

We're really excited about this, because it not only allows us to really customize curricula, but it also allows us to take a more holistic approach to education.

What was the origin of the J&J Institute? How was the idea created?

Bacci-Walsh: What we've seen internally are synergies among the different areas. The target audience may be different, but there are some things that are just universal in terms of, say, faculty- development or trying to find the right simulation or doing some procedures in an outpatient setting. We've seen some of those synergies internally, and we've said, 'how can we bring this to our external audience

as well? How do we keep getting better and better in terms of this holistic approach?'

What we had in the past was we had [education programs] like the Ethicon Institute or we had a DePuy Synthes Institute. And although we were all part of the same company, we didn't act that way. And now we truly say, 'how can we help our customers best?'

The Johnson & Johnson Institute recently announced a collaboration with the Federal University of Pernambuco and Hospital das Clínicas de Pernambuco in Recife, Brazil to train residents in minimally invasive surgery. Can you talk about how that fits into the program?

Bacci-Walsh: We [have had] an institute in São Paulo [since 2010], and one of the tenants of the institute is to give greater access to training to many surgeons in rural areas that may not have it. Some of our institutes in [for example] India or in Brazil allow us to bring that education to certain groups who may not have that access to it so easily.

Within North America, is there a need to get some of these training opportunities out into more places or are you still focused on the big cities?

Bacci-Walsh: We are finding that there are unique regional needs, so our professional education team is organized such that we have a national team [to run] the courses held at our institutes, but we also have a regional team that can bring the education to the surgeon. We sometimes will use a mobile truck [with training and simulation equipment] that we drive up to an academic institution or a hospital and allow nurses and PAs and surgeons, residents, fellows – throughout the day when they have an opportunity – to come to us and to get some hands-on training.

That's one of our objectives, for sure. In addition, we have jnjinstitute.com, where we make available little snippets of videos. A surgeon in a rural area, let's say, may not have done a procedure in a while, and he or she may want to refresh themselves around the approach or the procedure, so they may take a look at the video, to just refresh their memory. And that's been a great way to really augment the hands-on training by using this interactive digital experience.

How do you explain to the rest of J&J why the J&J Institute is worthwhile and what are the metrics you use to show that its helping the company overall?

Bacci-Walsh: Our Center of Excellence determines where there may be gaps in education. For example, in orthopedics, the anterior approach to hip replacement is an area that is new over the last ten to 20 years – taking that anterior approach versus a posterior approach.

A surgeon who's been in practice for a while may not have had that experience when they were a resident and fellow, so we provide them this opportunity to augment the education and expertise that they already have. We look at areas of need and decide if it is an area we need to focus. And of course, everything we do is driven by our credo.

Is there anything else going on that we should be paying attention to or looking forward to as the next big thing that's going to happen with the J & J Institute?

Bacci-Walsh: We're always evaluating new technologies. We'd love to get to a point where there are simulators that really allow us to, like I said, bring that education at the right time for the right surgeon in a way that is extremely cost-effective and can reach a surgeon no matter where they are in the world. That's something we continually strive for.

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Puerto Rico Tax-Haven Status, R&D Credit Weakened By Tax-Reform Bill

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While several device firms and Puerto Rico officials lobbied Senators hard in November to include a provision in the tax-reform bill to allow Puerto Rico to be considered a "free-trade zone," the bill passed Friday night by the Senate did not include the provision, making it less appealing for medical product firms to operate businesses there if the bill becomes law.

The GOP leadership in Congress is expected soon to choose members for a conference committee to iron out differences between the House tax bill, passed Nov. 17, and the Senate version of tax reform.

A "total of at least 50 medical device firm plants producing over 1,000 different medtech products are located on the island," FDA Commissioner Scott Gottlieb told Congress at an Oct. 24 congressional hearing. *(Also see "US FDA's Gottlieb Warns Congress Of Shortages, Potential Job Losses In Puerto Rico" - Medtech Insight, 25 Oct, 2017.)*

Among the device companies that have built facilities in Puerto Rico over the last 20 years are **Abbott Medical Optics Inc.**, **Baxter Corp.**, **Becton Dickinson & Co.**, **Boston Scientific Corp.**, **Cardinal Health Inc.**, **CR Bard Inc.**, **CooperVision Inc.**, **Edwards Lifesciences Corp.**, **Ethicon Inc.** (subsidiary of **Johnson & Johnson**), **Integra Neurosciences**, **Medtronic PLC**, **Roche Diagnostics Corp.**, **St. Jude Medical Inc.**, and **Stryker Corp.**

Those companies and future medtech US firms planning to build in Puerto Rico are likely to face a less favorable tax climate, under the current tax reform bill moving through Congress. Revenues earned at all medical product facilities – device, pharmaceutical, and diagnostics companies – represent more than 30% of Puerto Rico's gross domestic product, according to Gottlieb.

As approved by both the House and the Senate, a section in the Tax Cuts and Jobs Act would place a excise tax of 20% on foreign-made goods by US-based firms, including the devices that are being made at many medtech companies' Puerto Rican-based facilities. *(Also see "Medtech To Benefit From 20% Corporate Rate, Tax-Free Foreign Transfers In Pending US Tax Bill" - Medtech Insight, 17 Nov, 2017.)* The US tax code has been treating Puerto Rico as "foreign" for tax purposes, a fact that previously made the territory – where US companies currently pay only a local 4% excise tax – a much cheaper place for US firms to build plants than the US mainland, with its current 35% corporate tax rate.

Puerto Rico is also suffering the repercussions of a 10-year-long gradual repeal of the Internal Revenue Code's Section 936, which from 1976 to 2016, permitted US manufacturers to avoid corporate income on profits they made at plants in US territories (Puerto Rico, the Virgin Islands, and American Samoa) and sent home to a US parent firm. Former President Bill Clinton, a Democrat, signed a law that gradually phased out the Section 936 tax break between 2006 and 2016, because so many US firms were building plants in Puerto Rico that the US Treasury was losing tax dollars.

Unfortunately for the device firms with plants on the island, the current tax bill does nothing to restore Section 936, or any other similar provision giving Puerto Rico favorable tax status.

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With a reduced tax rate on foreign-made goods and recent repeal of the IRS's Section 936 that eliminated taxes on US plants in Puerto Rico, the territory will no longer be a tax haven under the GOP tax bill.

SOME FIRMS MIGHT LOSE RESEARCH TAX CREDIT

Another provision of the bill could cause medical product firms to lose out, is one of their most commonly-taken tax credits, the research and development (R&D) tax credit. The provision, which allows companies like pharmaceutical and device firms, to recoup the money they spend on innovation and development of new products, is under threat because many firms under the GOP tax reform bill will find themselves having to pay their taxes under the alternative minimum tax (AMT) rate of 20%.

While the AMT is seldom-used under current tax law, in which most companies must pay a 35% tax rates after deductions, with the newly-proposed tax rate of 20%, more firms will find themselves having to go the alternative minimum tax payment route; under the AMT, the R&D tax credit doesn't apply.

"Mistakes like this one happen when senators cut their deals 24 hours before the bill passes," Russ Sullivan, a former Senate staffer now with law firm McGuire Woods LLP, told the *Wall Street Journal* over the weekend.

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US FDA Chief Favors LDT Approach In Bucshon-DeGette Bill

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The traditional device approval process is a "poor fit" for laboratory developed tests, FDA Commissioner Scott Gottlieb told Congress at a Nov. 30 check-in hearing on implementation the 21st Century Cures Act. Gottlieb added that FDA staff will continue to offer technical assistance to help refine a "Diagnostics Accuracy and Innovation Act" defining new regulations for LDTs. His comments came at a hearing before the House Energy and Commerce Health Subcommittee.

"There is an opportunity to fashion a new regulatory framework, through the appropriate legislation, that will be a better fit for the kind of technology we're talking about here," Gottlieb said, after acknowledging Rep. Larry Bucshon's "thanks" for FDA's technical assistance in shaping the draft DAIA developed by Bucshon and Rep. Diana DeGette, D-Colo., last March. *(Also see "Diagnostics Reg Overhaul Floated In US House" - Medtech Insight, 21 Mar, 2017.)*

The draft Bucshon-DeGette bill creates a new regulatory category, distinct from devices, combining *in vitro* diagnostics and laboratory-developed tests, and involving at least two agencies – CMS and FDA – and the states in their continued regulation. LDTs are assays developed by sophisticated clinical laboratories and offered as in-house clinical testing services.

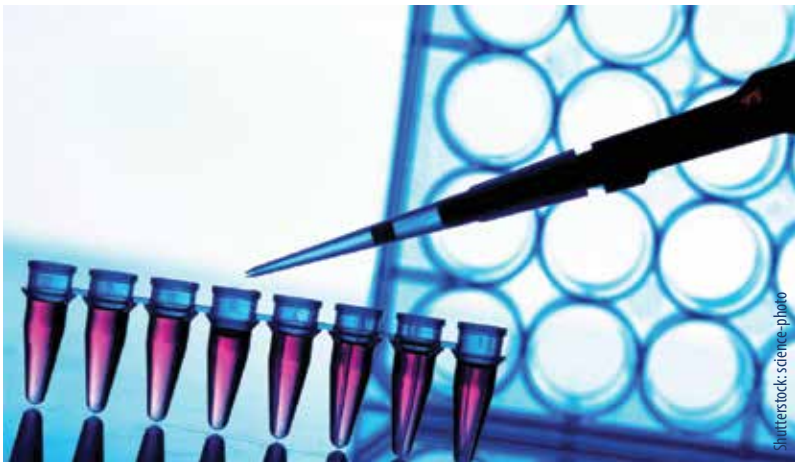
Last spring, the American Clinical Laboratory Association sent a letter of endorsement for the underlying concepts in the bill, although it also wanted existing tests to be grandfathered in, and be allowed enforcement discretion, under the existing FDA regulation system. IVD test-makers, represented by AdvaMedDx, said they could lend their support to the overall bill. *(Also see "Lab Professionals Oppose Draft Dx Reform Bill; Lab, IVD Industry Ready To Work With Congress" - Medtech Insight, 13 Apr, 2017.)*

DAIA RELIES ON FDA, CMS AND STATE REGULATORY ROLES

Bucshon said, "We believe the DAIA takes the best of what the FDA, CMS and states have to offer, and creates a new regulatory paradigm, building on the regulatory capacity of these critical entities."

Gottlieb has been forward since taking on the commissioner role that he believes a new approach that involves FDA oversight is needed for LDTs, and he has offered some loose ideas of what specifics he might support. *(Also see "Q&A Exclusive: FDA Commissioner Talks About His Tenure, Recruiting And LDTs" - Medtech Insight, 7 Nov, 2017.)* The agency is also rolling out creative approaches to voluntary regulation of advanced diagnostic services before any type of over-arching framework is established. *(Also see "A New York Minute: US FDA Leverages State's Health Department To Expedite NGS Reviews" - Medtech Insight, 15 Nov, 2017.)*

Gottlieb noted at the hearing, that for a long time, FDA has relied upon enforcement discretion when dealing with LDTs.



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At the hearing, Gottlieb acknowledged the technical assistance FDA has been offering on the DAIA draft legislation, and wants Congress to move ahead with it.

"But as we see these technologies become more sophisticated and more important to the practice of clinical medicine, and we see some variability in the quality of products patients are using and when physicians make important medical decisions, we *do* think FDA has a role to play in certain aspects of these products."

"The need to do that is now, so we will supply all the help and technical support you need – including the white paper we put out – that laid out some of our thinking on this," Gottlieb added.

The FDA LDT white paper Gottlieb referred to, was released early in the year, on Jan. 13, and offers ideas for Congress to shape a new regulatory system for LDTs. The paper calls for a risk-based approach to oversight of the tests, independent premarket review for certain tests, a focus on analytical and clinical validity, adverse event reporting and a robust laboratory quality system, among other details. *(Also see "FDA Passes The Buck On LDTs, But Floats Ideas" - Medtech Insight, 13 Jan, 2017.)*

DeGette also pressed Gottlieb on providing more technical assistance to her and Bucshon's staff on the bill, right after the new year.

"Mr. Gottlieb, we really want to get going on this, early in the new year, and quicker we can get more technical assistance, the better," the congresswoman said.

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US FDA Willing And Ready To Approve Novel Cardiac Troponin Assays

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US FDA wants to work with all stakeholders and developers of cardiac troponin assays to increase the availability of such tests that work, according to agency reviewer Paula Capisino. Capisino, from FDA's division of toxicology and chemistry, in the Office of In Vitro Diagnostics and Radiological Health, spoke at a Nov. 28 FDA workshop on regulatory challenges surrounding the tests.

The agency offered its perspective on troponin clinical trials at the Silver Spring, Md., workshop, including pre-analytical and analytical considerations.

Troponin is a protein in blood, which at high levels can point to heart muscle death, predicting myocardial infarction. Emergency room physicians routinely use troponin assays to help determine if patients are suffering a heart attack.

"Sometimes we hear ideas about FDA's expectations, or restrictions on these devices, that are not true," Capasino commented. "For example, there's an idea that we're not open to high-sensitivity performance devices, or that we mandate clinical cut-offs that sponsors are allowed to use – again, not true," she added.

FDA approved its first high-sensitivity cardiac troponin test, Roche's *Elecsys Troponin T Gen 5 STAT*, in January. *(Also see "Cardiac Troponin Assays Will Get US FDA Attention At November Workshop" - Medtech Insight, 1 Aug, 2017.)*

Companies have also increased focus on developing point of care, rather than central laboratory, troponin assays, but some have suggested some confusion about FDA standards. For example, **Trinity Biotech PLC**, developed point-of-care troponin tests (*Meritas Troponin-I Test* and *Meritas Point-of-Care Analyzer*, but withdrew its 510(k) submission in early October 2016, after the agency said the tests did not meet validation expectations. Jim Walsh, Trinity's chief scientific officer, said at the time that while the Meritas' point-of-care tests had "excellent performance characteristics," the agency had set a narrower temperature range and the assays failed to meet FDA's validation expectations. *(Also see "Trinity Pulls 510(k) For Troponin Point-Of-Care Test" - Medtech Insight, 4 Oct, 2016.)*

Other firms that compete in the cardiac troponin space are **Beckman Coulter Inc.** (*Access AccuTnI*) and **Abbott Laboratories Inc.** (*i-STAT*).

WIDE VARIATIONS CHALLENGE TRIALS

Vast variations in troponin levels in men and women of different ages and ethnicities who come into emergency room departments showing signs of myocardial infarction make it difficult for clinical trial designers to set cut-off levels of troponin that clearly show that a heart attack has occurred.

Fred Apple, a clinical lab director and professor at the University of Minnesota, said he would "put the onus on manufacturers" to develop trials of their troponin cardiac assays that recruit a minimum of 300 men and 300 women to get at some of these variations.

"But sometimes we see vast variations [of troponin levels] within these groups," Apple said, "so it's never clear where these cut-off numbers come from." Also, for those who want to use existing cut-off levels for devices already cleared, manufacturers can't be sure where the numbers came from, he added. "Is it FDA-driven, or is it manufacturer-driven?" Apple asked.

"Sometimes I have patients who have three-, four- or five-times the levels of troponin that is above the 99th percentile, who don't have MI [myocardial infarction] – it's one of those issues that needs to be resolved," said James McCord, a cardiologist with the Henry Ford Health System, Detroit.

VITAMIN B7 (BIOTIN) USE FOUND TO INTERFERE WITH ASSAYS

As workshop participants discussed some

FDA Safety Communication On Biotin (Vitamin B7)

A Nov. 28 FDA safety communication alerted laboratory professionals, lab test developers, health professionals and patients that biotin, which is sold over-the-counter as a beauty aide, can lead to clinically significant errors in lab test results. FDA has seen an increase in reported adverse events, including one death, related to biotin interference with a lab test.

For example, the alert noted that FDA had received a report that patients taking high levels of biotin died following falsely low troponin test results, when a troponin test known to have biotin interference was used.

The agency said it was aware of people taking up to 650-times the recommended daily intake of biotin, and some physicians may be recommending that patients with multiple sclerosis (MS) should take high levels of biotin.

Laboratorians were advised to communicate with clinicians, nurses and patients about their biotin use, and for those collecting troponin samples in the lab, ask whether the patient is taking biotin.

Health-care providers were advised to talk to patients about any biotin supplements they might be taking, including those marketed for hair, skin and nail growth, and to be aware that many lab tests – including cardiovascular diagnostic and hormone tests that use biotin technology, might be potentially affected. The alert said there is no safe level established for biotin in the blood for patients who are being tested – and the length of time for biotin clearance from blood is unknown.

Patients were advised to talk to their doctor if they use biotin about the possibility of interference.

of the barriers to clinical trial development for an assay used on patients who usually present symptoms only on an emergency basis, FDA reviewers Kerry Welsh and Brittany Schuck point to another, newer challenge: increased use of Biotin, or vitamin B7 supplements. It can interfere with troponin levels, making troponin cardiac assays less effective, they noted.

"Biotin is increasingly marketed as a beauty supplement, to improve appearance of nails and hair. Tabs are available over-the-counter at 10 milligrams or higher, but we believe many consumers at well above the daily recommended amount," Welsh said. "The issue with it, is that Biotin in the blood can interfere with the Troponin test," she added.

FDA issued a Safety Communication on Nov. 28 stating that Biotin may interfere with several laboratory tests and "cause incorrect test results which may go undetected." (See box.)

"I think it's obligatory on the manufacturer to identify if the clinical trial population may have had Biotin interference, especially among the 99th percentile population. And it should be on the package insert, and that's something that we as laboratorians have to make sure the clinicians understand," Apple said.

"Laboratorians *have* to be sure the package insert language on Biotin is followed, echoed Rob Christensen, medical director, point-of-care tests, University of Maryland.

WHO LEADS IN SETTING TROPONIN ASSAY GUIDELINES?

FDA's Capisino enumerated the many challenges to good clinical-trial designs for troponin cardiac assays, among them: getting timely informed consent from an emergency-room population; confusion and disagreement over clinical cut-offs; biases related to study design and study execution; and missing samples – or samples not labeled with a timepoint when they were collected.

Jackie Wienecke, a reviewer in FDA's Office of In Vitro Diagnostics division of chemistry and toxicology commented, "I think what we have today, is not a perfect trial design, with an 'all-comers' design, but it's the best we have right now.

"But for manufacturers, what we'd like them to understand, is that if you use exclusion criteria to design a trial, then those patients will not be part of your intended-use population."

"I think we really need to define what the FDA role is," responded Allan Jaffe, a clinical cardiologist with Mayo Clinic. "Do you really want FDA to make the clinical guidelines to define what is a risk for you? I would argue, we probably don't."

He added, "I'm not sure we want FDA to make the final determination, as to what the cut-offs are, which protocols we use, what the deltas are – I think that's asking them to do what we who set the guidelines [at the American College of Cardiology] are doing."

Jaffe added that FDA's job should be limited to reviewing the assays, and determining if they work, and if they are safe. "The rest of the details, as nice as they might be, are things we ought to take over at the American College of Cardiology."

"And we would love that help," one of the FDA reviewers responded.

NEXT STEPS

"We're going to take this information we heard today back to FDA, and talk about further conversations we can have, and what further topics need to be explored," said Courtney Lias, director of FDA's OIR division of chemistry and toxicology devices.

"But it's clear to me, we at FDA have not done a good enough job of giving our perspective on things, such that we might dispel rumors of what would, or wouldn't be acceptable. We need to make sure people understand that we want what's good for patients, and what's good for doctors, and what's needed to give them the support they need."

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3D-Printing Final Guidance Clarifies Manufacturing Practice Expectations

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A finalized leap-frog guidance on technical considerations for 3D printing isn't a major change from the draft version, but it does clarify FDA's expectation for removing manufacturing material residue in additive manufacturing processes.

FDA issued the draft guidance in May 2016 as part of an effort to get ahead of the inevitable boom in additive manufacturing to support manufacturing of devices, make more personalized medical technology and create 3D models that surgeons can use to enhance procedures. *(Also see "FDA Tackles 3-D Printing Considerations In Draft Guidance" - Medtech Insight, 12 May, 2016.)*

"[Additive manufacturing] is a rapidly growing technology that is frequently used for product research and development in many industries, and for commercial production in some industries (e.g., aerospace, medical devices)," states the guidance. "While many AM technologies exist, at the time of publication of this guidance, the most commonly used technologies in medical devices are powder bed fusion, stereolithography, fused filament fabrication, and liquid-based extrusion."

One of the few changes in the final guidance re-states the term "cleaning and sterilization" in the draft to "removing manufacturing residues and sterilization." The agency says this was done to add more clarity about its expectation of manufacturers. *(Also see "US FDA Works To*

Finalize 3D Printing Guidance; Industry Asks For More" - Medtech Insight, 14 Jun, 2017.)

"The FDA wanted to clarify what the agency meant by the need to remove manufacturing material residues from 3D-printed devices. This term is more appropriate based on its description in the medical device regulations," said James Coburn, senior research engineer at FDA's Center for Devices and Radiological Health. "Manufacturers might confuse the term 'cleaning' with final device cleaning and sterilization, which was not the FDA's intended use of the word and we did not want to create confusion."

WORKSHOP FOLLOW-UP

As FDA was developing its final guidance, the agency held a workshop earlier in the year to hash out some of the nuances of additive manufacturing technology and how the agency should oversee the industry, specifically in the application of creating 3D anatomical models. The biggest issue that was raised during that meeting was lack of consensus and clarity around the segmentation process. *(Also see "3D-Printed Anatomical Models: Clinicians, Companies Hash Out Issues" - Medtech Insight, 25 Sep, 2017.)*

Segmentation is the process by which radiologists aggregate images of body parts acquired through scans and use them to render 3D models from those images. Stakeholders during the workshop argued more controls and improvements are needed to ensure the models are accurate and useful.

In a response to *Medtech Insight*, Coburn notes the final guidance tries to help explain FDA's thinking on segmentation by addressing the level of acceptable image quality and ability to recreate the same models from those images. He adds the issue pertains to the larger context of any imaging used for 3D-printed medical devices and not only to anatomic models.

In concluding the earlier workshop, FDA and the Radiological Society of North America stated they would put together a white paper with recommendations for additive manufacturing. Coburn says RSNA has held conference calls with stakeholders who expressed interest in contributing to the white paper and FDA is also helping draft the document.

There were several other issues that were raised during the workshop, including implementing a certificate program for radiologists and clinicians to ensure they are qualified to produce and use 3D models. There was also some contention between FDA and industry stakeholders about the definition of intended clinical use of the 3D models. Clinicians and manufacturers disagreed about whether requiring an intended use to be stated for additive manufacturing printers would hamper their ability to tailor the technology to individual patients' needs. FDA did not touch on either issue in the final guidance and specifically said the certification issue is outside its scope.

FDA's Gottlieb says the agency is working to establish a regulatory framework based on existing laws and regulations to oversee traditional manufacturers and non-traditional manufacturers, such as academic institutions.

GOTTLIEB: 'TIP OF THE ICEBERG'

FDA Commissioner Scott Gottlieb also issued a statement in step with the release of the final guidance. He noted to date the agency has reviewed more than one hundred devices already on the market that were made using 3D printers, including patient-matched anatomical devices such as knee and facial reconstruction implants. The commissioner also noted FDA last year approved **Aprecia Pharmaceuticals Co.**'s *Spritam* seizure drug, which has a more porous matrix making it better at dissolving and taking effect faster. *(Also see "How 3D Printing Can Enhance And Expand Medtech Opportunities" - Medtech Insight, 7 Sep, 2017.)*

"This is likely just the tip of the iceberg given the exponential growth of innovative research in this field," said Gottlieb. "We envision that burn patients in the near future will be treated with their own new skin cells that are 3D-printed directly onto their burn wounds. Further down the road, there is the potential for this same technology to eventually be used to develop replacement organs."

He, however, emphasized the leap-frog guidance is only intended to give stakeholders an initial understanding of FDA's thinking on the topic, especially since it is such a rapidly evolving field and the agency's recommendations are likely to evolve with the technology.

"We are already seeing the beginning of this evolution as hospitals and academic centers use their own 3D printers to create innovative dental implants, replacement knee joints, and experimental heart valves and bone implants for use in clinical studies," added the commissioner. "An increasing number of surgeons across the country have been saving infants born with a life-threatening breathing condition by creating patient-matched 3D-printed splints to install in their patients' tiny airways, which expand and degrade as the babies grow."

Gottlieb says the agency is working to establish a regulatory framework based on existing laws and regulations to oversee traditional manufacturers and non-traditional manufacturers, such as academic institutions.

"Developing a transparent policy on 3D printing remains an important next step for us, and we plan to explore the role of nontraditional manufacturing facilities like a hospital operating room or university laboratory," he added. "The FDA also plans to review the regulatory issues related to the bioprinting of biological, cellular and tissue-based products in order to determine whether additional guidance is needed beyond the recently released regulatory framework on regenerative medicine medical products."

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It's Here! New, Pivotal EU Medical Device Coordination Group Surfaces

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The most pivotal new organization formed out of the new Medical Device and IVD Regulations has just been set up. During its first meeting on November 28, the EU Medical Devices Coordination Group (MDCG), focused on the most pressing implementation issues under the new Regulations and on organizational issues.

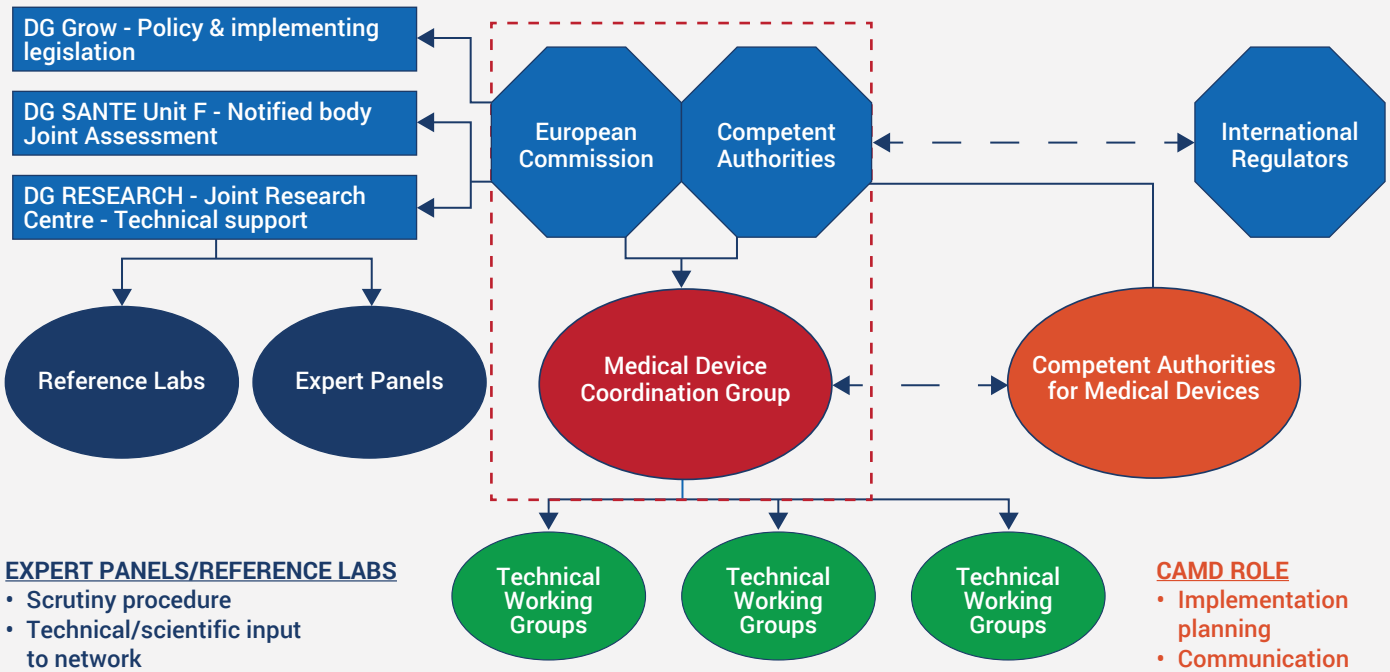
The MDCG will have a range of responsibilities focused on the successful implementation of the new rules and an ongoing role related to high-level decisions on all aspects of the new Regulations. Its responsibilities will include:

- Assessment and designation of notified bodies and other notified body-related activities;
- Scrutiny of high-risk devices;
- Borderline decisions;
- Contribution to the development of Common Specifications and scientific guidelines, including product-specific guidelines, on clinical investigation of certain devices, in particular, implantable devices and class III devices;
- Assisting the member states in their coordination activities in particular, in the fields of classification and the determination of the regulatory status of devices, clinical investigations, vigilance and market surveillance; and
- Provision of scientific, technical and clinical opinions and advice.

Its full list of responsibilities, including a comprehensive listing of duties under the title provision of scientific, technical and clinical opinions and advice, are set out

How The MDCG Is Connected

The MDCG effectively lies at the center of initial medical device implementation activities and ongoing responsibilities, as outlined in this table.



EXPERT PANELS/REFERENCE LABS
- Scrutiny procedure
- Technical/scientific input to network
- Advice to innovators
- Common specification
- Verify claimed performance of IVDs (class D)
- Batch testing
- Development of testing & analysis methods for market surveillance
- Reference materials

MDCG TASKS
- Oversight
- Guidance development
- System development
- Policy advice

TECHNICAL WORKING GROUPS
- Classification
- Clinical
- EUDAMED
- Notified bodies
- Market surveillance
- Vigilance
- Standardisation/CTS

CAMD ROLE
- Implementation planning
- Communication
- Best practice development
- Training
- Peer review
- Joint actions
- Coordination
- Strategic development

in Chapters VIII of the MDR and IVDR (Articles 105 and 106 of the MDR and Article 99 of the IVDR).

WHO DOES WHAT ON THE MDCG?

The group comprises medtech expert representatives from the competent authorities and effectively replaces the Medical Devices Expert Group (MDEG), which had been made up of representatives from the authorities and other stakeholders, including industry and notified bodies.

The exclusion of industry has been a source of contention for manufacturers, but the Regulations make it clear that the MDCG will set up subgroups to gain access to necessary in-depth technical expertise. These subgroups may also comprise industry and other stakeholders (MDR, Article 103,7; IVDR, Recital 83).

The European Commission will chair the MDCG but not take part voting. It will also provide a framework for the competent authorities to exchanges experiences, as well as providing technical, scientific and logistic support to the MDCG and its subgroups.

The Commission will also organize the meetings of the MDCG and its subgroups, participate in those meetings and ensure the appropriate follow-up.

GETTING THE MDCG OFF THE GROUND

Setting up the MDCG is understood to be the subject of one of the most pressing of the 118 Implementing and delegated acts that are due to be published as a means to fully implement the MDR and IVDR.

The MDR and IVDR make it clear that the MDCG has to establish its rules of procedure, including:

- The adoption of opinions or recommendations or other positions, including in cases of urgency;
- The delegation of tasks to reporting and co-reporting members;
- The implementation of Article 107 regarding conflict of interests; and
- The functioning of sub-groups.

The newly set-up EU Transitional Measures Taskforce will clarify the role of the MDCG in governance, as part of a high-priority work item within the Commission' roadmap for implementing the MDR and IVDR. This work will include publishing guidance outlining MDCG roles and responsibilities.

SOME INITIAL DUTIES

One of the first matters that will come before the new group for consideration is endorsing the best practice guide recently issued by the European Commission's Notified Bodies Oversight Group. The document addresses the designation and notification of conformity assessment bodies under the MDR and IVDR.

The MDCG will also work with the Commission to draw up the urgent plan for the implementation of the specifications related to the new Eudamed medical device and IVD database.

Medtech Insight understands that a Commission internal validation process will now follow. After that, the MDCG should be included in the Commission's Register of Expert Groups and Other Similar Entities. For each expert group, the register provides information, including on the Commission department which is running the group, as well as on its members and its mission and tasks. The register also identifies relevant documents that are produced and discussed by the groups.

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EU Notified Body Designation Process: 20-Month Wait Is Not Good News

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The latest 16-page guide from the EU Notified Bodies Operations Group – NBOG BPG 2017-1 – has come as a harsh reality check for medtech companies looking to stay ahead of new compliance deadlines. Anyone who thought that the urgent need for notified bodies to be designated against the EU's Medical Device and IVD Regulations would mean an accelerated review by the designating authorities will be disappointed.

The procedures and timelines are outlined in NBOG's Best Practice Guide (BPG) on the designation and notification of conformity assessment bodies against the MDR and IVDR. The document suggests that, even for notified bodies that have already applied for designation in the last few days, the final decision by designating authorities is unlikely before July 26, 2019 – 20 months from now.

The guide also suggests that any notified body designated under the medical device directives and aiming for designation under the new Regulations should apply at least 18 months in advance of the relevant Directive (Active Implantable Medical Devices Directive, Medical Devices Directive, or IVD Directive) being repealed to ensure continuation of their activities under the new legal framework.

Keeping with these timelines (see the flowchart below for more details) will likely be critical to the success of the implementation of the MDR and IVDR, given concerns over the lack of timely availability of notified bodies and experts to staff them.

Apart from outlining anticipated timelines, the NBOG guide aims to:

- Provide guidance to the authorities responsible for notified bodies (designating authorities) and joint assessment teams (JATs) when conducting designation assessments of conformity assessment bodies

(CABs) that apply for designation as a notified body in the field of medical devices and/or IVDs; and
- Bring consistency and align the working practices of the different designating authorities in the Member States regarding the assessment, designation and notification of CABs.

STEPWISE PROCESS

According to a flowchart presented in the document, national designating authorities should be able performed the initial "completeness" checks on applications by notified bodies within 30 days of the application dates. This means the applications that were submitted on the first possible day, Nov. 26, could go to the European Commission's Directorate General for Health and Food Safety Directorate F (Sante/F), which will be coordinating the processes, by December 27.

Sante/F will acknowledge its receipt via email to the designating authority, informing also the European Commission's Directorate-General Internal Market, Industry, Entrepreneurship and SMEs, Directorate D (GROW/D), which oversees medical devices and IVDs and, specifically, the new Medical Device Coordination Group. MDCG is to play a fundamental implementation role, including in the designation of notified bodies.

Having finished the "completeness" check, the national designating authorities will then turn to reviewing the application and supporting documentation, according to its own procedures. There is no time limit established in the MDR and/or IVDR for this review, although the estimate is that this detailed assessment could take between three and eight weeks after the completeness check.

The outcome of this subsequent exercise is then to be documented, preferably in English, in the preliminary assessment report (Form NBOG F 2017-5 or NBOG F 2017-6), which must be forwarded to the Sante/F. (See box to the right for a listing of relevant forms and documents.)

The European Commission's receipt of this preliminary assessment report will then trigger the appointment of a JAT, and the subsequent scheduling of the corresponding on-site assessment. Therefore, it is of the utmost importance, the best-practice guide notes, that the designating authority makes sure the outcome of the review is "sufficiently satisfactory as to substantiate the conduct of an on-site assessment."

Sante/F will also immediately transmit the preliminary assessment report to the MDCG.

ON-SITE ASSESSMENT

Formal announcement and arrangement of practicalities for the on-site assessment by the JAT – generally made up of one expert from Sante/F, who will act as JAT coordinator, and two national experts (from EU member states that are different from where the applicant conformity assessment body hails from) – should then be possible by June 13, 2018, for the notified bodies among the first applicants.

While there is no time limit set in the MDR and IVDR for scheduling the on-site assessment, following receipt of the preliminary assessment report, Sante/F will liaise with the designating authority to seek preliminary agreement on dates for the on-site assessment.

The main criterion determining the order of the on-site joint assessments will be the precise time of receipt of the preliminary assessment report in Sante/F's electronic mailbox.

The first on-site assessments are likely to start on about Sept. 10. The duration of an on-site assessment will depend on the size of the conformity assessment body and the applied-for scope of designation, but, typically, according to the guide, they will require 40 hours or, in the case where no interpretation is needed, 32 hours.

Sante/F will propose national experts who are best suited, on the basis of their field of competence and expertise in relation to the conformity assessment body's applied-for scope of designation and language capabilities, and are available to participate effectively in the on-site assessment.

The JAT will be expected to provide its final opinion on the first applications for designation by about June 5, 2019, according to the NBOG flowchart, some 50 days before the final decision on designation is expected from the national designating authority.

LANGUAGE ISSUES

The NBOG guide notes that the language that each application is made available

Relevant Forms And Documents

The following documents are relevant to either notified bodies making the application for designation (NBOG F 2017-1-4) or to designating authorities recording the results of its preliminary assessment of the notified body (NBOG F 2017-5-6):

- NBOG F 2017-1 rev. 2 Application form to be submitted when applying for designation as a notified body under the medical devices Regulation (MDR)
- NBOG F 2017-2 rev. 2 Application form to be submitted when applying for designation as a notified body under the in vitro diagnostic devices Regulation (IVDR)
- NBOG F 2017-3 Applied-for scope of designation and notification of a Conformity Assessment Body form – Regulation (EU) 2017/745
- NBOG F 2017-4 Applied-for scope of designation and notification of a Conformity Assessment Body form – Regulation (EU) 2017/746
- NBOG F 2017-5 Preliminary assessment report form – Regulation (EU) 2017/745
- NBOG F 2017-6 Preliminary assessment report form – Regulation (EU) 2017/746

For more details, see: EU Commission Issues A Last-Minute implementing Regulation For Notified Bodies.

Notified Body Designations: A Flowchart

The table below sets out the timelines and procedures for conformity assessment bodies (CAB) or existing notified bodies to be designated as notified bodies under the MDR and IVDR and it also shows, on the right-hand side, the likely fastest times in which designation is possible.

TENTATIVE TIME-LINE	ACTIVITY / TENTATIVE DATE FOR EXISTING NOTIFIED BODIES
18 months in advance of repeal of relevant Directive	**Activity:** Application sent to the designating authority from the CAB **Date:** Nov. 27, 2017
Within **30 days** of receipt of the application	**Activity:** Completeness check of application by the designating authority **Date:** Dec. 27, 2017
Immediately after application is considered complete	**Activity:** Transmission of application to Sante/F **Date:** Dec. 27, 2017
Estimate: within **2 months** after application is considered complete	**Activity:** Assessment of CAB's application by the designating authority and issuing of preliminary assessment report **Date:** Feb. 27, 2018
Within **14 days** after receipt of preliminary assessment report	**Activity:** Appointment of the joint assessment team (JAT) and scheduling of the on-site assessment **Date:** March 13, 2018
Within **90 days** after appointment of the JAT	**Activity:** Formal announcement and arrangement of practicalities for the on-site assessment; dissemination of information to JAT members; assessment of CAB application by the JAT **Date:** June 13, 2018
At least **5 weeks** *before* the anticipated on-site assessment	**Activity:** Coordination teleconference between the JAT and the designating authority **Date:** July 20, 2018
On-site assessment	**Activity:** In accordance with the agreed assessment plan **Date:** Sept. 10, 2018
Last day of the on-site assessment	**Activity:** Designating authority list of non-compliances and summary of the JAT assessment to be presented at the closing meeting **Date:** Sept. 14, 2018
Timeframe defined by the designating authority	**Activity:** CAB's submission of the CAPA (corrective and preventive action) plan **Date:** September/October 2018
Within 30 days after the on-site assessment	**Activity:** JAT remaining diverging opinions to be sent to the designating authority **Date:** Oct. 14, 2018
Estimate: **within 2 months** after the on-site assessment	**Activity:** Designating authority's confirmation and assessment of CAB's CAPA plan. To be forwarded to the JAT **Date:** Nov. 14, 2018

Source: NBOG BPG 2017-1

will usually align with the official language of the relevant member state, but the notified body applicant should also include copies of any documents that are already available in English. This includes, in particular, the quality manual, procedures relating to qualification of personnel, and procedures relating to the process of conformity assessments. If these documents are not available in English, the notified body may provide copies translated into English to facilitate the joint assessment, the guide suggests.

Where a national designating authority submits the preliminary assessment report in a language other than English, Sante/F will arrange for a machine translation (or, time permitting, an official translation), which will also be transmitted to the MDCG.

Moreover, if the on-site assessment is to be conducted in a language other than English, or the relevant documentation to be reviewed is not available in English, Sante/F will arrange for interpretation to be provided at the European Commission's expense. The guide notes that up to four interpreters may be required for each on-site assessment.

The preference for English as the working language is peppered throughout the NBOG guide. It can be expected that where documents, reports or forms are not in English, frequently, they will need to be translated to facilitate communication with assessors and members of the MDCG who will come from any of the 27 (or 28, including the UK) member states of the EU.

FORMAL APPROVAL NEEDED FROM NEW MDCG

Before the guide – officially, NBOG BPG 2017-1 – is formally applicable it needs to be endorsed by the MDCG, which was due to be set up by November 26 under the new IVDR and MDR to play a vital governance, administrative and implementation role. The MDCG has to agree on the relevant steps and deadlines where it is involved in this and any future BPGs

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QMS And Lab Accreditations Allow Russian Regulator To Green Light Eurasian Device System

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A recent agreement on quality management systems (QMS) was the last of the second-level Eurasian Economic Union (EAEU) requirements needed before the EAEU medical devices regulatory system can be used in practice. This major, essential piece of the EAEU medical device system that tells manufacturers how to comply with QMS for the whole region was published as a Decision by the Eurasian Commission in October.

QMS is the last of the 13 second-level documents/requirements number. And the timeframe for two of the 10 third-level documents is 2018 – the rest were due in 2016. *(Also see "Russian Medtech Industry Wants Quicker Progress On Eurasian Bloc Plans – 2017 Now Targeted" - Medtech Insight, 24 Feb, 2017.)*

Local medtech regulatory expert Alexey Stepanov reports that the Decision (No. 134 – link in Russian) makes the implementation, development and maintenance of QMS mandatory for the registration of sterile class IIa, class IIb, and class III devices. Other classes of devices – class I (low-risk) and non-sterile class IIa – do not formally require QMS. Nevertheless, having it in place would lead to simplified amendments and/or re-registration procedures, which would subsequently be subject to notification instead of assessment.

A manufacturer's QMS is subject to inspection audits for each of its stated manufacturing sites by accredited EAEU organizations. Manufacturers may use any of them, regardless of where they are located in the EAEU member-state territory – in much the same way as the EU notified body system of auditing and conformity assessment operates. After an initial audit, post-registration QMS assessment inspections are required every three years. Unscheduled inspections are also provided for.

TRANSITIONAL ARRANGEMENTS

The full EAEU system for devices is not scheduled to be in place and functioning until 2022. Officially, after Dec. 31 2021, local processes will no longer be allowed. However, deadline extensions have not yet been discounted. *(Also see "Eurasian Union For Medtech Gathers Pace, But Barriers Hamper Timely Completion" - Medtech Insight, 15 Aug, 2017.)* And there will be a 12-month transition during which QMS will not be mandatory for device registrations, Stepanov notes. If a QMS inspection audit has not happened within two years of registration, submission of an ISO 13485 certificate will provide a presumption of conformity with registration requirements.

Checklists for QMS subsystems are contained in the Decision text, and refer to requirements on design and development controls, document change controls, corrective and preventive actions, production and process controls and consumer-related processes.

ACMP REGIONAL REGULATORY BODY

The Eurasian commission also adopted, on Oct. 26, Decision No. 123 (link in Russian), which lists the regulations pertaining to the EAEU Advisory Committee on Medical Products (ACMP). This is a new regional consultation and regulatory body responsible for addressing any differences of approach and decision-making in matters of medical device registration assessment that may arise between Eurasian member states. There is likely to be considerable need for its services, especially in the early days of the system, given the scope for disputes between the reference member state and those in the role of mutually accepting decisions.

Nevertheless, there is noticeably more momentum in the EAEU's medical device regulatory project than a year ago. The sense of forward motion is augmented considerably by the news that two Russian labs have been accredited by the regulator, Roszdravnadzor (RZN), to work on EAEU device applications. And during an RZN Eurasian regulatory seminar on Oct. 27, it was confirmed that manufacturers may begin to apply for device testing according to the new requirements, noting the separate requirements for technical and biological-safety testing.

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CONTINUED FROM PAGE 1

According to **Ivantis Inc.** which developed the *Hydrus Microstent* MIGS device, currently in US clinical trials, in the US alone about 20% of 3.7 million people undergoing cataract surgery have a concurrent diagnosis of glaucoma. The World Health Organization estimated that by 2020, 32 million cataract surgeries will be performed worldwide, and will include millions of people diagnosed with glaucoma. In the US, about 740,000 patients may be candidates for MIGS treatment, Ivantis said in a recent press release.

GLOBAL MARKET OVERVIEW

According to Meddevicetracker's "Ophthalmic Surgical Product Market," the global market for ophthalmic surgical products, which is divided into four segments – ophthalmic surgical systems, IOLs, MIGS devices and surgical instruments – is expected to rise from $7.5bn in 2016 to $9.4bn by 2021, a CAGR of 4.6% *(Also see "Ophthalmology Surgeons, Companies Finding Solutions In Medtech" - Medtech Insight, 18 Sep, 2015.)* (See Figure 1.)

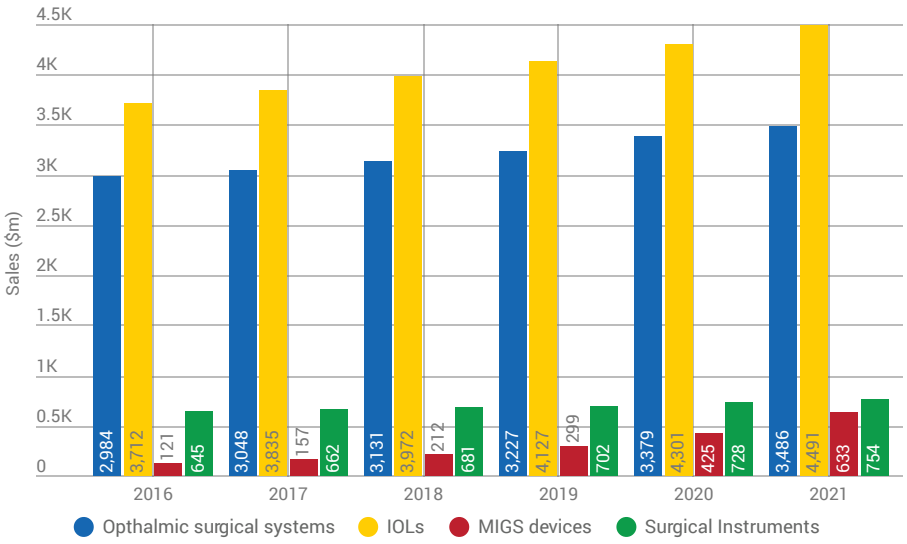
Ophthalmic surgical systems, which include diagnostic systems and laser/phaco energy-based surgical therapy systems, make up the largest segment, but is expected to see the slowest growth from $3bn in 2016 to $3.5bn in 2021, a CAGR of 3.2%. The same growth percentage is expected for the third-largest segment, surgical instruments, rising from $645m in 2016 to $754m by 2021 *(Also see "All Eyes On Ophthalmic Devices Market" - Medtech Insight, 14 Jul, 2015.)*.

IOLs, the second-largest segment in the overall ophthalmic surgical market, is expected to see only modest growth from $3.7bn in 2016 to $4.5bn, a CAGR of 3.9%. However, despite single-digit growth, the surgical equipment, instruments and IOL segments are experiencing a moderate rebound compared to the past few years, reflecting pent-up demand and improving economies. The new emerging MIGS market will see the biggest growth from $121m in 2016 to $633m by 2021, a CAGR of 39.2%, driven in large part by addressing the shortcomings of glaucoma medications, which include non-compliance and side-effects, as well as those of laser or non-invasive surgical therapies. (See Figure 2.)

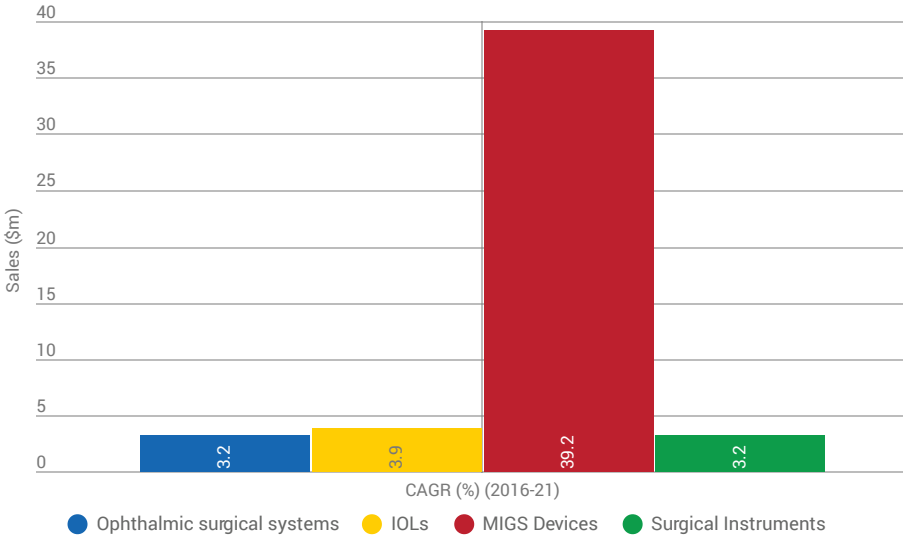
FIGURE 1

Ophthalmic Surgical Product Sales, ($m)

Combined Market Forecast, 2016-2021



CAGR Percentage, 2016-2021



Totals may not sum due to rounding. This forecast assumes that no major adverse events or product recalls will negatively impact the market. IOLs = intraocular lenses; MIGS = micro-invasive glaucoma surgery

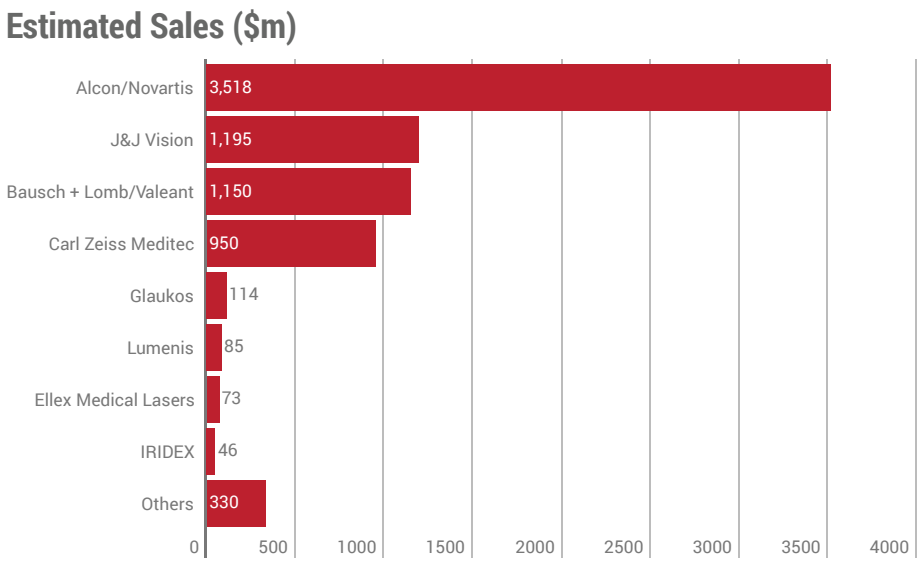
Source: "Ophthalmic Surgical Product Market," Meddevicetracker

ALCON

Alcon Inc., a division of **Novartis AG**, dominated the global market in 2016 with a share of more than 47% based on sales of $3.5bn. Swiss giant Novartis has been realigning its operations in recent years to grow the troubled Alcon division. After underperforming in FY 2016 due to a lag in surgical segment revenues, the company finally posted revenue

FIGURE 2

Ophthalmic Surgical Products Market, Estimated Global Share By Supplier, 2016



Notes: Others include: A.R.C. Laser GmbH, HOYA Surgical Optics, HumanOptics, LENSAR, Lenstec, "Ophthalmic Surgical Product Market," Meddevicetracker

growth in Q2 2017; surgical revenue – including sales of IOLs – increased 3% that quarter, while vision care went up 2%, the first surge of growth in that division since 2014.

Novartis said it considered exiting the ophthalmology business, but after re-aligning its business to focus on eye care said it will decide whether to leave the eye care business or not by the end of 2018, at which point the company is expected to have entered the next growth phase. For now, it'll invest heavily in innovation.

Three of Alcon's largest competitors – **Johnson & Johnson Vision Care Inc.** (previously **Abbott Medical Optics Inc.**), **Bausch + Lomb/Valeant Pharmaceuticals International Inc.** and **Carl Zeiss Meditec AG** – contributed 44% of sales in 2016, amounting to more than $3bn in combined revenues with each player contributing 16%, 15% and 13% of sales respectively.

BAUSCH + LOMB

Valeant Pharmaceuticals, a $10bn pharmaceuticals and medical device firm, also offers a vast portfolio of eye care products, including contact lenses, IOLs and ophthalmic surgical devices through Bausch + Lomb, which it bought in 2013. In FY 2016, Bausch + Lomb reported $4.607bn in revenues, essentially flat over revenues of $4.603bn in 2015. The division doesn't report segmented surgical ophthalmic sales, but it is estimated that this portfolio contributes slightly more than $1bn annually in global sales, the majority of which comes from US sales.

Like its competitor, Alcon, Bausch + Lomb also banks on internal development of innovative products to grow its business. The company also expects to continue to benefit from the 2017 launch of ophthalmic surgical systems, including the *Stellaris Elite* and *Vitesse*.

Bausch + Lomb is developing a unique ophthalmic viscosurgical product that will protect the corneal endothelium during the phaco emulsification process of cataract surgery, while improving chamber maintenance and lubrication during IOL delivery.

JOHNSON & JOHNSON VISION

Johnson & Johnson entered the surgical ophthalmic devices space with the acquisition of Abbott Medical Optics (AMO) in February 2017 for more than $4.3bn, which strengthened its position in cataract surgical laser systems and laser refractive surgery. AMO is a leading manufacturer of IOLs.

In FY 2016, AMO had global sales of $1.2bn including products in three segments: cataract surgery, laser refractive surgery and consumer eye health.

Before AMO was bought, it launched several new products in FY 2015 including the *TECNIS Monofocal 1-Piece IOL* with the *TECNIS iTec Preloaded Delivery System* and the *Whitestar Signature PRO* phaco system for removing cataracts, both systems are sold in the US.

CARL ZEISS

After reorganizing its ophthalmic business in 2016 by combining the previous two strategic business units, ophthalmic systems and surgical ophthalmology, into one unit that encompasses the entire ophthalmic portfolio with the goal to optimize sales, increase market penetration and grow globally, the Carl Zeiss Meditec Group increased revenues for the fiscal year ended Sep. 30 in 2016 by nearly 5% to €1.1bn compared to the prior year. In FY2015/2016 ophthalmic devices posted combined total revenues of €791.9m compared to €747.2m in the prior fiscal year, driven mostly by refractive laser systems.

In the refractive laser surgery market, parent company, Carl Zeiss Meditec AG benefitted from the FDA approval and launch of the minimally invasive *SMILE* procedure, in the US last September, which uses the *VisuMax* femtosecond laser for correcting myopia.

The company hopes to grow through innovation and plans to invest 10-11% in R&D annually.

SMALLER PLAYERS

Several smaller competitors, including **Lumenis Ltd.**, **Glaukos Corp.**, **Ellex Medical Lasers Ltd.** and **Iridex Corp.**, contributed about 1% each with Glaukos contributing 1.5%. Other smaller manufacturers contributed roughly $330m, or 4.4% of total sales.

Though Glaukos' market share is small relative to the major companies, Meddevicetracker expects that the pioneer in the MIGS segment will be able to steadily increase its market share over the forecast period amid robust demand for its *iStent* technology, rising international sales and continued innovation leveraging its MIGS technologies.

In the last three years, Glaukos has seen steady growth. In FY 2016, it reported net sales of more than $114m, an increase of nearly 60% over $72m in sales in FY 2015. The company launched the first iStent in 2012, following US FDA approval and is steadily increasing its portfolio.

Glaukos, however, will be facing stiff competition from Alcon, which acquired a competing MIGS device called *CyPass Micro-Stent* from **Transcend Medical Inc.**

Emerging innovative players that are also now playing in this market segment include Ellex Medical Lasers and Ivantis, among others.

Australian-based Ellex Medical Lasers is a small, but rising competitor in the ophthalmic laser segment. In FY 2016, the company posted record high sales of nearly $73m, up $10.2m from FY 2015. The growth was driven in large part by rising global sales, especially in China, and a positive response to its ab-interno canaloplasty (*ABiC*) three-step MIGS procedure for reducing IOP in glaucoma patients, using its flagship *iTrack microcatheter*.

The iTrack is the only approved MIGS device in China, which is a key growth market, and Ellex has extension of approval until May 23 2022.

Another small device maker, Irvine, California-based Ivantis Inc. developed the *Hydrus Microstent* for reducing IOP in treating primary open-angle glaucoma. Mountain View, California-based **Iridex Corp.** is a $40m ophthalmic medical technology company specializing in medical laser systems and associated instrumentation. Its core product, the *MicroPulse* laser technology, addresses glaucoma and retinal diseases. Israel-based **Lumenis Ltd.** markets the *SLT laser therapy* for treating open-angle glaucoma.

MIGS

MIGS devices are among the fastest-growing technologies for treating refractive mild to moderate glaucoma by reducing IOP and the progression of glaucoma. MIGS devices serve an unfulfilled niche given that current treatments -- eye drops that have shown poor compliance by patients and have side effects; laser therapy, which has shown high failure rates; and the gold standard of surgery, trabeculectomy – are no longer seen as valid options for the majority of patients, according to Meddevicetracker.

Since it involves placing a permanent implant into the eye, MIGS avoids the major issue plaguing glaucoma medication of patient non-compliance, providing a less-invasive, safe, and effective therapy to prevent permanent vision loss for refractory glaucoma patients.

While these technologies are new and therefore require more thorough clinical study evaluation, including comparison studies to evaluate which new competitive MIGS therapy is most efficacious, the MIGS segment is expected to see tremendous growth in the coming years.

Glaukos

Currently, more than half a dozen companies are directly competing in the MIGS space, which was pioneered by the $100m Glaukos Corp., which, up until last year, was the only company with a US FDA-approved MIGS device *(Also see "Glaukos' Micro-Bypass Stents Work As First-Line Glaucoma Therapy" - Medtech Insight, 26 Sep, 2016.)*

The company launched the first-generation iStent in the US in mid-2012 and outside of the US, the next-generation MIGS systems *iStent inject* and *iStent supra* received the CE mark in 2010, and is now being sold in Australia, Canada, Germany, South Korea and Taiwan, among other countries.

James Murphy, a glaucoma specialist at the Eye Center of Southern Connecti-

TABLE 1

Selected New And Emerging Microinvasive Glaucoma Surgery Implants And Technologies

COMPANY	MIGS IMPLANT	APPROVALS	UNIQUE FEATURES
Alcon/Novartis	CyPass Micro-Stent	FDA August 2016	Ab-interno insertion into the supraciliary space
Allergan	XEN Gel Stent	CE mark 2013; FDA November 2016	first approach to create pathway for aqueous flow from the anterior chamber to the subconjunctival space to create a filtering bleb
Ellex Medical Lasers	iTrack microcatheter/ ABiC procedure	FDA 2013	only MIGS device to comprehensively open up all of the components of the eye's natural outflow system
Glaukos	iStent	FDA 2012/ first FDA-approved MIGS device	trabecular micro-bypass stent
iStar Medical	MINIject	Pursuing CE mark	iStar technology; biocompatible medical-grade silicone with a porous geometry to promote bio-integration to increase drainage
Ivantis	Hydros Microstent	Expected FDA approval 2018	first "intracanalicular scaffold" for treating primary open-angle glaucoma
InnFocus Santen Pharmaceuticals	MicroShunt Glaucoma Drainage Systemq	CE mark 2012	micro-tube works by shunting aqueous fluid from anterior chamber of the eye to a subconjunctival/sub-Tenon flap to lower IOP

Source: Company websites

cut in New Haven, Connecticut said he's been performing MIGS procedures since the iStent came to market in 2012 and is also now using the newer Alcon CyPass Micro-Stent.

He said he uses the iStent predominantly in patients with mild glaucoma and the CyPass mainly in patients with moderate glaucoma, but also sometimes in patients with mild glaucoma.

"I sometimes offer endoscopic cyclophotocoagulation (ECP) in conjunction with iStent implantation as it can offer additional IOP-lowering potential as it reduced the eye's production of aqueous fluid whereas the iStent aims to increase aqueous outflow via Schlemm's canal – it's all about lower in's and higher out's," Murphy told *Medtech Insight*.

Brian Chen, a glaucoma specialist from the Acuity Eye Group in Los Angeles, said he's been able to lower patients' dependence on eye drop medications as well as lower IOP when performing ICE procedures (iStent combined with cataract surgery and ECP) compared to doing cataract surgery alone in glaucoma patients who need cataract surgery.

"In mild to moderate glaucoma (patients) who are uncontrolled or even controlled, but have problems with eye drops, I offer the ICE procedure," Chen told *Medtech Insight*. "When glaucoma patient also need cataract surgery, I can make the most of ICE."

The iStent is designed to reduce IOP in the eye and restore natural fluid outflow by the trabecular micro-bypass method, creating a permanent bypass between the front part of the eye and its natural drainage pathway through the primary blockage site of the trabecular network. It has shown to reduce patients' reliance on glaucoma medication, with the majority of iStent patients in the US pivotal trial remaining medication-free at 12-month follow-up.

The company is leveraging its iStent technology to develop a next-generation pipeline, which includes four new products: the iStent inject, the iStent supra, the *iDose* and the *iStent infinite*.

Murphy said he's excited about the iStent inject, which he expects will be easier to use than the iStent, and with that will open the door of use by comprehensive ophthalmologists.

> "I think when *iStent inject* comes out, it will be a little easier for a comprehensive ophthalmologist to use these devices in combination with cataract surgery, so that'll maybe encourage more use of MIGS amongst comprehensive ophthalmologists with ease of use," says James Murphy, a Connecticut-based glaucoma specialist.

"I think when iStent inject comes out, it will be a little easier for a comprehensive ophthalmologist to use these devices in combination with cataract surgery, so that'll maybe encourage more use of MIGS amongst comprehensive ophthalmologists with ease of use," he said. It's easier to use, if you're not familiar with angle surgery, he added.

For the iStent inject, Glaukos has developed two versions that are currently being studied in clinical trials: one injector with preloaded stents is being tested to evaluate safety and efficacy in lowering IOP in patients in conjunction with cataract surgery and the other is being tested to assess efficacy as a standalone treatment for lowering IOP.

The iStent supra drains the suprachoroidal space. The iDose with a travoprost intraocular implant is a drug delivery system that is implanted in the eye in a microinvasive procedure to continuously deliver medication for extended periods of time to lower IOP.

An international study of 30 subjects (including 27 who endured prior trabeculectomies) showed that three iStents implanted in a standalone procedure provided a 52% reduction in mean IOP to 13.7mmHg at 12-month follow-up. Additionally, over the same time period, patients achieved a 77% reduction in the mean number of topical medications, from 1.83 preoperatively to 0.43 postoperatively. The company is planning to submit an IDE filing with the FDA in Q4 2017 to conduct a one-year study of about 65 patients. Provided study results are successful, Glaukos will seek 510(K) clearance for the iStent infinite.

Preliminary results of a three-year-long Phase II study of 154 patients comparing two models of iDose delivery systems using different travoprost elution rates compared to topical timolol maleate ophthalmic solution (0.5%) showed an approximate 8mm Hg reduction rate in mean IOP in both models of the iDose Travoprost systems after nine months post-op. The safety profile was also favorable with no incidents of hyperemia. The company said it will re-

view the results with the FDA in Q4 2017 and commence Phase III trials in early 2018.

Alcon/Novartis

While Glaukos is benefiting from substantial growth thus far, it will face strong competition in the next five years from startups but also from Alcon, which has a strong sales force and the marketing clout to bring products to health-care providers.

Meddevicetracker expects that more of the innovative smaller players will be swallowed up by big ophthalmic surgical product makers firms as seen with Alcon's 2016 acquisition of the CyPass Micro-Stent from Transcend Medical or Allergan's 2016 buyout of the XEN Gel Stent from AqueSys.

Alcon's CyPass Micro-Stent received FDA approval in August 2016 and available in the US; in the EU it was introduced in April 2017. The device is indicated for treating patients with mild to moderate primary open-angle glaucoma in conjunction with cataract surgery or as a standalone procedure in patients with primary open-angle glaucoma who have failed previous medical treatments.

The CyPass Micro-Stent is the first MIGS device to leverage an entirely new outflow pathway for excess aqueous fluid in the eye - the supraciliary space, which is the space between the sclera, the white outer layer of the eyeball, and the ciliary body. Once implanted, it creates a permanent conduit between the anterior chamber of the eye and the suprachoroidal space to improve the eye's natural drainage pathway, according to Alcon (see Video 2).

The device was approved by the FDA based on the COMPASS study, the largest MIGS trial to date, Alcon said.

The multicenter, controlled pivotal COMPASS trial of 505 patients, who were randomized to receive either phaco and CyPass Micro-Stent implantation (n=374) or phaco alone (n=131), showed at two-year follow-up that about 73% of eyes treated with the CyPass Micro-Stent achieved a ≥20% reduction in IOP, compared to only 58% of eyes treated with phaco alone. Additionally, about 61% of eyes treated with the CyPass Micro-Stent achieved the target IOP (an unmedicated diurnal IOP between 6mmHg and 18mmHg) versus only 43.5% with cataract surgery alone, according to the study's lead investigator, Steven Vold. The CyPass Micro-Stent has been clinically proven to be 32% more effective in lowering IOP than cataract surgery alone, the author wrote.

Murphy said in his experience the CyPass can function similarly to an iStent.

"It just gives a little bit additional reduction to intraocular pressure or gives you IOP that is almost the same as traditional glaucoma procedures," he said. He said that he may also use the CyPass in patients with mild glaucoma and very elevated intraocular pressure.

"I find that you can get a greater reduction in IOP with the CyPass versus the iStent," he noted.

According to Murphy, some glaucoma specialists have also seen that CyPass may offer a greater reduction in IOP in patients that are near-sighted, but patients that are far-sighted can have a slight myopic shift when CyPass procedures are performed in conjunction with cataract surgery, which is undesirable.

Allergan

Allergan Inc. paved its way into the MIGS device market with the acquisition of *AqueSys's XEN Gel Stent*, which received US FDA approval in November 2016 for the surgical treatment of refractory glaucoma. The device has been commercially available in the US since early 2017 and received the CE mark in 2013. It is also available in Canada, Switzerland, and Turkey; more than 10,500 implants have been distributed worldwide.

The system, which includes both the XEN Gel Stent and preloaded disposable *XEN Injector*, is implanted via the ab-interno approach. The miniature gel stent is implanted via a small corneal incision, and effectively reduces IOP by creating a new drainage channel with a permanent implant that becomes flexible.

Chen said essentially the Xen Gel Stent is an ab-interno trabeculectomy. But he said he would prefer using the XEN Gel Stent over performing traditional trabeculectomy with his advanced glaucoma patients. To date, XEN Gel Stent is not reimbursed, which he said, is the biggest issue for him. He's also waiting for more clinical data.

The company claims that its device has a competitive advantage, because the XEN Gel Stent drains to the subconjunctival space, and is the first procedure that creates a low-lying, ab-interno bleb in refractory glaucoma.

The XEN Gel Stent is indicated for managing refractory glaucoma where previous surgical treatment has failed, or in patients with primary open-angle glaucoma and pseudoexfoliative or pigmentary glaucoma with open angles who are unresponsive to maximum tolerated medical therapy.

The US FDA approval was based on the success of the US pivotal trial, in which XEN reduced IOP from a mean medicated baseline of 25.1mmHg (±3.7mmHg) to 15.9mmHg (±5.2mmHg) at 12-month follow-up (n=52) in 65 patients with refractory glaucoma. In the trial, the mean baseline number of IOP-lowering medications was 3.5 (±1.0) versus an average use of 1.7 (±1.5) medications at 12 months. In the primary analysis, nearly 80% of patients achieved a ≥20% reduction in diurnal IOP on the same or fewer number of medications compared to baseline.

Ivantis

Irvine-based Ivantis touts its *Hydrus Microstent* as the world's first "intracanalicular scaffold" for treating primary open-angle glaucoma, which is currently limited to only three treatment options: eye drops, laser therapy and surgery.

Hydrus is the only device that dilates and reconstructs the Schlemm's canal, the primary pathway where fluid exists in the eye. The device is implanted in a quick outpatient procedure via extremely small incisions used in cataract surgery. Unlike traditional surgical procedures to treat glaucoma, no additional incisions are required, resulting in a significantly less invasive approach, termed ab-interno, which is believed to result in fewer complications and faster healing than traditional glaucoma surgery.

Murphy said he's excited about the prospects of the Hydrus Microstent.

"Hydrus (Microstent) may just open up more real estate of Schlemm's canal compared to iStent, which may or may not translate to an increased reduction in intraocular pressure after implantation of the Hydrus (device)," he said. The device is currently being evaluated outside the US in both cataract surgery and standalone glaucoma surgery and Murphy said he's waiting for clinical trial results to better evaluate the device.

Ivantis submitted Hydrus for FDA approval on October 31, and disclosed the headline results from its US HORIZON trial in conjunction with the American Academy of Ophthalmology (AAO) annual meeting in New Orleans, which took place from Nov. 11-14, 2017.

The HORIZON study enrolled 556 patients across 38 centers in nine countries and included patients with mild-to-moderate primary open-angle glaucoma who were randomized to receive cataract surgery and the Hydrus implant or had cataract surgery alone. The study's primary endpoint was reduction in mean diurnal IOP from baseline at 24 months following medication washout.

At a 24-months efficacy cross comparison study, 77% of cataract surgery patients who were also treated with Hydrus achieved a greater than 20% reduction in unmedicated IOP, which compares to 53% of iStent patients who also had cataract surgery in the Gen 1 investigational study.

After seeing the headline data, Wells Fargo's Larry Biegelsen wrote in his analysis on Nov. 13 that the efficacy data on HORIZON on the surface looks better than Glaukos' Gen 1 iStent investigational device exemption trial, "which is consistent with the anecdotal feedback from our physician checks though confounders (e.g. patient washout) and varying study designs make it somewhat difficult to cross compare between studies."

"Anecdotally, physicians with whom we've spoke perceive Hydrus to be more effective than iStent Gen 1 but harder to implant," Biegelsen wrote. "We would expect GKOS' second-generation device, iStent Inject, to close the efficacy gap with Hydrus." He added, however, that it is currently difficult to compare the two devices, because the Inject data he reviewed is in a standalone setting, without cataract surgery.

"Anecdotally, physicians with whom we've spoke perceive Hydrus to be more effective than iStent Gen 1 but harder to implant," Wells Fargo analyst Larry Biegelsen says. "We would expect GKOS' second generation device, iStent Inject, to close the efficacy gap with Hydrus."

He expects that Hydrus' device could be FDA approved in mid-2018, if not slightly earlier.

"Our assumption continues to be that Hydrus will be approved a few months ahead of iStent Inject," he wrote. He expects the Hydrus to capture 5% of the US MIGS market in 2018, assuming the company will market the device on its own.

Ivantis closed a $25m Series C financing in January 2017, led by new investor RA Capital Management, and included new investor Mérieux Développement. The company said it plans to use the funds for commercialization.

InnFocus

The *MicroShunt Glaucoma Drainage System*, developed by Miami, Florida-based **InnFocus Inc.**, is the first minimally invasive standalone procedure for treating mild, moderate and severe primary open-angle glaucoma, which potentially represents a core advantage over other MIGS technologies, because it does not require simultaneous cataract removal.

The device gained the CE mark in 2012 and has been implanted alone or in combination with cataract surgery in clinical trials outside the US in patients diagnosed with early- to late-stage glaucoma where it showed a mean post-operative IOP below 15mm Hg, representing a reduction of 50% in IOP after three years of follow-up.

The device is about the size of an eyelash and is made out of material that has been used for 15 years in drug-eluting coronary stents. It is in late-stage clinical trials in the US and Europe and is the world's only randomized trial comparing its safety and efficacy against trabeculectomy, the gold standard for lowering IOP.

iSTAR Medical

Belgium-based **iStar Medical SA**'s first-generation device is the *STARflo Glaucoma Implant*, made of iSTAR's material, developed at the University of Washington, Seattle, a micro-porous drainage system that increases the eye's natural uveoscleral outflow. It is implanted via

an ab-externo surgical procedure derived from trabeculectomy, the most common glaucoma filtering surgery.

iSTAR is now leveraging its *STAR technology* through its next-generation product, the *MINIject*, a MIGS device designed to significantly reduce IOP by improving aqueous humor outflow from the anterior chamber to the suprachoroidal space. In April 2016, iStar Medical raised 10m Euros in a Series B financing, which will support further development and fund its European clinical study, geared to achieving the CE mark.

The company announced on Oct. 27, 2017 it completed enrollment of 25 patients with mild to moderate open-angle glaucoma for its international study to assess safety and performance of the device as measured by IOP reduction at six months.

Ellex Medical Lasers

Ellex Medical Lasers Ltd.'s *iTrack microcatheter*, which was FDA approved in 2013, is the only illuminated miniaturized microcatheter designed for performing MIGS that is used to viscodilate Schlemm's canal during the ab-interno canaloplasty (*ABiC*) procedure.

ABiC claims to be different from other MIGS procedures in that it preserves tissue, doesn't damage tissue and doesn't require a permanent implant in the eye. It also doesn't leave behind a shunt or stent. It also claims to be the only MIGS system to comprehensively open up all of the components of the eye's natural outflow system: the trabecular meshwork, Schlemm's canal, the Collector Channels, and distal outflow system.

According to the company, 228-eye 12-months case series data reported an average reduction in mean IOP of 30% with a 50% reduction in medication burden. Ellex reported nearly 30% growth in revenues for the iTrack in FY 2016 with sales of more than $6m. Ellex acquired iTrack from **iScience Interventional Corp.** in 2013.

MIGS PROS AND CONS

Murphy and Chen both agreed that at least in their experience, MIGS has shown very little risks for patients.

> "I think the MIGS procedures have filled a treatment gap between topical therapy and traditional SLT, and the traditional glaucoma procedures that was lacking. It's a big leap to make from eye drops to trabeculectomy or glaucoma drainage implants, and MIGS has fulfilled a need in between these extremes over the last 15 years," Murphy says.

"I've never had to follow up post-op any more than I would just follow up a regular cataract patient," Chen said about performing ICE procedures. He said on occasion patients may have increased inflammation post-surgery or a little bleeding from the iStent procedure.

"The downside or risks of having a MIGS procedure performed are pretty small whereas the downside or surgical risks of a traditional surgical glaucoma procedure are pretty major," Murphy said.

MIGS patients normally wouldn't be considered for traditional surgery. Murphy said he performs traditional surgery in patients that either have severe glaucoma and need a big reduction in intraocular pressure or in patients that have had MIGS procedures that failed.

"The greatest disadvantage is that sometimes they fail (MIGS)," Murphy said. "Sometimes you don't get a reduction in intraocular pressure. If you qualify failure as no additional reduction in intraocular pressure over what you'd expect for cataract surgery or even pre-operatively for an IOP, then it could be even up to 30 or 40%."

"I approach glaucoma in a step-wise fashion in which you offer the less invasive procedures first (MIGS), and if those don't leave you with an IOP you are happy with, one can consider the more invasive traditional glaucoma procedures," he said, adding "It is not so easy to go the other way."

"I think the MIGS procedures have filled a treatment gap between topical therapy and traditional SLT, and the traditional glaucoma procedures that was lacking. It's a big leap to make from eye drops to trabeculectomy or glaucoma drainage implants, and MIGS has fulfilled a need in between these extremes over the last 15 years," Murphy said.

At the same time, current MIGS devices are far from perfect, according to glaucoma specialist who declined to be named.

"Devices that enable us to increase outflow with minimal intervention and get good enough drops in pressure are obviously going to be quite desirable, so the ideal device hasn't been made yet," the specialist said.

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