Medtech Insight
Issue 59
medtech.pharmamedtechbi.com
Pharma Intelligence Informa
September 4, 2017

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EYE ON THE PRIZE: Drug Delivery Advances To Fuel Ophthalmic Drug Market

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After decades of research, there are only a handful of approved ocular drug delivery systems in the US at present, all of them to treat disorders of the back of the eye such as cytomegalovirus (CMV) retinitis, uveitis, wet age-related macular edema (AMD) or diabetic macular edema (DME). Front-of-the eye drug delivery systems to treat conditions like glaucoma – one of the biggest cause of blindness – are still not available on the market, although several candidates are currently in clinical trials.

"There has been lots of work in creating these various drug delivery systems, but not much regulatory success, in my opinion," said Gary Novack, founder and president of San Rafael, California-based **PharmaLogic Development Inc.**, which provides development expertise to pharmaceutical and medical device companies. "It is harder than it looks. There are greater challenges to [drug delivery within] ophthalmology than some of the systemic medicines administered through dermal patches."

For instance, the eye is a limited space to insert therapy. There are also restrictions as to what fits comfortably and safely in the eye. "We have a rather narrow range of excipients, pH and tonicity that can be used even for simple eye drops," Novack said. Additionally, human ocular pharmacokinetics is rarely feasible. "In other words, we cannot sample eye tissue in humans the same way blood is sampled for systemic medicine," Novack said.

Novack believes that both the anterior and posterior segment of the eye present great opportunity and need for drug delivery systems. For instance, the most common chronic drug therapy for the front of the eye is for glaucoma; however, currently it requires that the patient or caregiver remember to administer the eye drops at least once a day and be able to do so correctly. "Less than one-third of chronic glaucoma patients at one private practice could properly put in eye drops," Novack noted.

Another chronic disease of the anterior segment is dry eye, also currently treated with eye drops. Additionally, there are other episodic ocular conditions like infections or seasonal allergic conjunctivitis that require treatment.

For the back of the eye, the current standard of care for wet AMD is frequent intravitreal injections, "which requires a lot from both the patient, who is typically

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UK focus
http://bit.ly/2xxO5iO
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Coverage of the highly anticipated UK Life Sciences Strategy, released Aug. 30. Also, the UK's device regulator issued an interactive guide to the new EU Medical Device and IVD Regulations.

Real-world evidence
http://bit.ly/2iLd6UG

US FDA finalized a guidance on how it will use real-world evidence to support decisions for medical devices, a central part of the device center's strategic priorities.

ESC highlights
http://bit.ly/2wnMzzy

One of the key European cardiology meetings of the year, the European Society of Cardiology Congress, took place in Barcelona on Aug 26-30. Find out what the key trial data highlights were.

Orthobiologics insight
http://bit.ly/2xMobqO

The global market for orthobiologics products is expected to reach $1.4bn in 2021. What are the factors driving growth and what are the challenges competitors in this field still must overcome?

Device Week
http://bit.ly/2v0IJtS

On our latest podcast, we discuss the implications of the recently enacted FDA Reauthorization Act. And look for a discussion of some of Medtech Insight's recent deep-dive market intelligence features in the upcoming episode of Device Week.

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Medtech insight

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specialist Dexcom President and CEO Kevin Sayer tells *Medtech Insight* the company plans to maintain its upward trajectory with a new addition to the leadership team, increased operational efficiency and expansion into new markets.

POLICY & REGULATION

Singapore's Priority-Review Scheme Goes Live

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Singapore's new priority-review scheme – designed to get medical devices registered and to market about 25% faster than the standard review procedure – went live today.

Eligible companies that want to apply to use the new scheme can do so as of Aug 22, according to the country's Health Sciences Authority, which has posted details for applicants on its website together with information on the fees that will apply.

The scheme is intended for devices that have not been approved outside Singapore and submitted to the HSA through the agency's standard, full evaluation route. Applicants should select the "Priority Review Scheme" section when they file for product registration via the agency's online medical device information and communication system, MEDICS.

The scheme cannot be used retrospectively for recently submitted marketing applications that would have otherwise qualified for priority review. It only applies to applications submitted on or after Aug. 22, HSA confirmed.

There are two routes available under the scheme. Route 1 is for a device that falls within one of five health-care categories – cancer, diabetes, ophthalmology, cardiovascular and infectious diseases – and is intended for an unmet clinical need.

Route 2 is for a device that does not meet the qualification criteria for Route 1.

The scheme is applicable to moderate-risk class B and C devices, and high-risk class D devices that do not incorporate therapeutic products. It does not apply to class A (low-risk) products.

Priority-review evaluation fees will, depending on the route chosen, be about 15% to 50% higher than fees charged for the standard full-evaluation procedure. (See Table 1.)

Regulatory and documentation requirements for priority-review applications are the same as those for a full evaluation under the standard review pathway, except they must include additional justification to support that the device fulfils unmet clinical needs for Route 1.

The HSA said its assessment of safety, quality and efficacy will not be compromised under the new scheme. "A shorter target turnaround time for priority-review applications is targeted through reduction of the evaluation queue time without shortening of the actual time required for evaluation of the application," it explained.

Earlier this month, industry experts told *Medtech Insight* that priority review applicants should be well prepared when selecting the scheme – information requests from HSA during the screening stage that relate specifically to the scheme's qualification criteria need to be responded to with full supporting documentation within two weeks. Missing the deadlines means an application will be withdrawn from priority review and be put into the normal review pathway, where standard turnaround times apply, the experts warned. The application could even be withdrawn in the case of non-response from the applicant. *(Also see "Medtech Associations Regulatory Networking, July 2017 – Singapore, the Philippines, Myanmar" - Medtech Insight, 7 Aug, 2017.)*

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TABLE 1

Priority Review: Turnaround Times And Fees

	TURNAROUND TIME (WORKING DAYS)		EVALUATION FEES (SGD$)		
EVALUATION ROUTE	STANDARD REVIEW	PRIORITY REVIEW	STANDARD REVIEW	PRIORITY REVIEW	
				ROUTE 1	ROUTE 2
Class B full	160	120	3,500	4,100	5,300
Class C full	220	165	5,700	6,600	8,600
Class D full	310	235	11,400	13,200	17,100

Source: Health Sciences Authority

Published online 08/22/17

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elderly and may require a caregiver to get them to the office, and the physician," Novack said.

Novack said the holy grail for wet AMD is longer lasting treatment that does not require monthly or every-other-month visits. "Many companies have tried extending duration of effect, but to date there are no approved products, although there are several in development," Novack said.

As diabetes becomes more prevalent, therapies for other retinal diseases like DME and diabetic retinopathy become more pressing, too. However, should back-of-the-eye drug delivery systems become successful, they will still face competition from off-label treatments prepared by compounding pharmacies, as well as lower-priced biosimilar products.

For both front- and back-of-the-eye products, "we will need to see if the US healthcare system will pay a premium for patient and physician convenience," Novack said.

Michael O'Rourke, an ophthalmic consultant for Scotia Vision Consultants LLC (Tampa, Florida) who specializes in drug delivery, agreed that cost and reimbursement are two factors that could impact adoption of novel ocular drug delivery devices. In spite of this, his outlook for the ophthalmic drug market remains very rosy. He predicts that globally, the ophthalmic drug market will double between 2015 and 2020 -- from $20.2bn to $30.5bn – with the largest increase in the retina market (from $9.3bn to $16.5bn), followed by the glaucoma segment (from $4.7bn to $6.1bn) and dry eye market ($3.1bn to $3.7 bn).

He believes that because the drugs themselves are already expensive, this might mitigate to some extent the cost argument against paying a premium for innovative devices to deliver these drugs. Additionally, patient preference could also be a strong driver for the uptake of these drug delivery systems. "If you ask patients if they would prefer to have their eye injected 12 times a year as opposed to an implant that is injected once or twice a year, the answer is a no-brainer," O'Rourke noted.

The safety profile of these drug delivery systems is also favorable. "Whenever you put a foreign body into the eye, you need to ensure that you do not cause any side effects, inflammation or unnecessary complications," O'Rourke said. "To date, approved implants have had acceptable safety records."

The vast majority of the expected growth in the retina drugs market is being fueled by two anti-VEGF drugs to treat wet AMD: ranibizumab (*Lucentis*) and aflibercept (*Eylea*). "A lot of companies in the retina drug space want to change their business model from patients needing frequent injections to sustained-release drug delivery therapy," O'Rourke said.

For the glaucoma market, daily eye drops of up to three different products present patient compliance challenges, which can be addressed with a slow releasing delivery system for up to one year. The same strategy is being pursued for the dry eye segment.

"Potentially, sustained-release drug delivery systems can provide better patients outcomes," O'Rourke said. "But additional data is required as to whether future products will achieve improved efficacy results."

In the rest of this article, Medtech Insight takes a look at some of the more promising innovations - and the companies behind them – in ocular drug delivery.

MULTI-YEAR DRUG DELIVERY

In September 2014, **Alimera Sciences Inc.** in Atlanta, received FDA approval of the *ILUVIEN* implant for DME in patients previously treated with a corticosteroid without a clinically significant increase in intraocular pressure (IOP). Of the four drugs approved to date for DME, "ILUVIEN is the only treatment that delivers therapy continuously for multiple years," said Ken Green, chief scientific officer for the publicly traded company.

The device releases 190 micrograms, an amount contained in a single typical steroid eye drop; in this case, corticosteroid fluocinolone acetonide, over three years. "Our delivery system is efficacious at these low levels because this particular steroid is extremely lipophilic; in other words, it penetrates tissue very effectively, as opposed to the other steroid, dexamethasone, approved for DME," Green said.

Alimera Sciences Inc's ILUVIEN Impact

ILUVIEN compared to a single grain of rice

Source: Alimera Sciences Inc.

The polyimide cylindrical tube that comprises ILUVIEN is 3.5 mm long and 0.37 mm in diameter, the equivalent space of fitting 32 ILUVIEN implants into a single grain of rice.

The implant is injected into the eye, just like a normal intravitreal injection, through a 25 gauge needle. "The needle is important because a 25 gauge needle leaves a self-sealing wound, so there is no stitch required," Green said.

ILUVIEN is injected through the pars plana and the implant settles near the bottom of the eye.

The implant itself is also nonbioerodable. "Right now, nonbioerodable technology is the only release technology that allows us to achieve extremely low and consistent release of therapy for a long period of time," Green explained. The implant remains intact within the eye and the physician can simply inject another one as needed. "We know from intraocular lens experience that the polymer used with ILUVIEN is biocompatible inside the eye," Green said.

So far, over 10,000 patients worldwide (of which 50% were in the US) have been implanted with ILUVIEN.

Recent clinical data show two DME patient groups being treated with ILUVIEN. Those previously treated with short-acting, anti-vascular endothelial growth factor (anti-VEGF) injections (average once every three months) had attained good visual acuity. However, after ILUVIEN was initiated, these patients required only one injection on average every 22 months. "The treatment burden for this group has

The ILUVIEN Applicator

The ILUVIEN Applicator with the micro implant in the window

Source: Alimera Sciences Inc.

Massachusetts Eye and Ear's Drug Delivery Contact Lens

Photo by: John Earle

decreased dramatically, while maintaining vision," Green said.

The second DME group had poor visual acuity or even visual decline with the other short-acting DME therapies. With ILUVIEN, though, the frequency of injections is reduced from every three months to every seven months. "This was still a significant reduction in frequency," Green conveyed. "These patients also see a moderate improvement in their visual acuity."

Green said ILUVIEN is a product that has the potential for multiple indications: RVO, posterior uveitis, diabetic retinopathy and wet AMD. "The real value of drug delivery in the eye is to achieve consistent delivery of therapy and minimize patient compliance," Green said.

CONTACT LENS FOR ANTERIOR DRUG DELIVERY

A contact lens embedded with medication is in preclinical stage at Boston Children's Hospital and Massachusetts Eye and Ear. The researchers have completed proof of concept, drug safety and efficacy studies with two different drugs: latanoprost for glaucoma and the steroid dexamethasone for postoperative inflammation.

The concept of delivering drugs via a contact lens is not new. "It was first proposed in the 1960s," said co-developer Joseph Ciolino, an ophthalmologist at Mass. Eye and Ear. "The challenge has been to load enough drug and release it in a time frame that is clinically relevant. Most attempts result in the drug being dispensed quickly. But with our design, we are able to load a lot of drug and control the release by introducing the drug polymer film embedded within the contact lens."

To the casual observer, the lens looks like any other contact lens, according to co-developer Daniel Kohane, director of the Laboratory for Biomaterials and Drug Delivery at Boston Children's Hospital. A small, thin ring-shaped polymer film situated on the periphery of the lens contains the drug in micrograms to milligrams quantity. "The ring not only releases the drug, but allows the patient to see right through it, so vision is not adversely affected," Kohane said. Lens breathability and hydration are also comparable to traditional contact lens.

In glaucomatous rabbits and monkeys, the latanoprost-containing contact lens delivered the medicine continuously for 1 month, achieving an average reduction in IOP of 6 mm Hg with a lower dose, which is equivalent to latanoprost eye drops. However, with the high dose, the pressure reduction nearly doubled to between 10 and 12 mm Hg.

"These high-dose results were surprising," said Ciolino.

For dexamethasone, very high levels of the drug were delivered to both the front and back of the eye in rabbit models, for a significant reduction in inflammation.

Both drugs are at the same level of development. A clinical trial involving both medications is planned within the next year.

Although the technology allows for a 30-day drug release, and even longer, it is expected that the contact lens will become commercially available for 1-week use only.

The contact lens notion is "very much a platform technology that could be adapted to a wide range of drugs, at least small-molecule drugs," said Kohane. "We also have data to suggest that our lens can be used to deliver a substantial amount of drug to the retina."

RESERVOIR IMPLANT

Genentech Inc. (South San Francisco, Calif.) has on ongoing Phase 2 study of the ranibizumab (*Lucentis*) port delivery system, which is a solid-state reservoir implant that is surgically placed in the part of the eye called the pars plana. The implant to treat wet AMD holds a small volume of highly concentrated drug that is slowly released, potentially over a 4- to 6-month period, or even longer. The device can then be refilled with fresh drug in the ophthalmologist's office with a custom needle that is part of the drug/device combination system.

"The goal of the Phase 2 study is to define the duration of the therapeutic effect between refills," said Jason Ehrlich, senior group medical director and global head of clinical ophthalmology for the company. "While we are currently studying the ranibizumab delivery system in patients with wet AMD, the underlying technology is also a platform, so the volume of the reservoir can be modified and the elution rate of drug out of the reservoir and into the eye can be modified for different sizes and types of molecules."

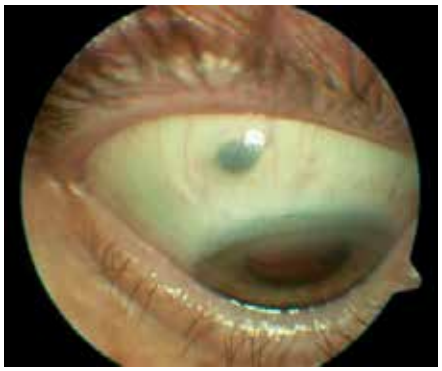
Genentech, a member of the Roche Group, acquired the technology from ForSight VISION4, when Roche purchased the company in January.

The delivery system, which is roughly the size of a grain of rice, is inserted using standard vitreoretinal surgical techniques. After the physician makes a small incision in the pars plana and the device is inserted through the incision, ranibizumab is initially loaded into the device via an injection needle, and the conjunctiva is then pulled back over the implant and secured in place, similar to typical 20-gauge vitreoretinal surgery. "The procedure takes a few minutes in the operating room, followed by a short recovery period for the patient," Ehrlich said.

Genentech is testing three different concentrations of ranibizumab in the delivery system to determine the pharmacodynamic relationship and the refill interval. "We know that VEGF is a very well validated and clinically important target in ophthalmology," Ehrlich said. "Our products and the other anti-VEGFs on the market have truly redefined what patient outcomes can be for these leading causes of blindness due to retinal vascular disease."

Ehrlich said the desired target for the ranibizumab port delivery system is 4 to 6 months between refills. "Undertreatment can be a significant issue for these retinal diseases," he said. "Our hope is that our technology will allow patients to receive the same benefits as they do now with anti-VEGF injections, but not need to come to the office as frequently," he said.

Genentech Inc.'s Ranibizumab Port Delivery System



Source: Genentech Inc

The refillable port is implanted in the pars plana. It is designed to deliver ranibizumab over a sustained period.

The entire market for retina therapeutics is large and growing, according to Ehrlich, because of an aging population and more patients being diagnosed and treated. To make the administration of ranibizumab easier, the drug recently became available in a 0.5 mg prefilled syringe as opposed to coming in a vial. "This eliminates many of the steps involved in preparing the product for the patient," Ehrlich said.

Ehrlich believes that the industry is on the cusp of a potential revolution over how ophthalmic drugs are delivered. "However, these delivery systems are not about convenience; they are about achieving the best outcomes for patients over the long term." One of the challenges, though, of efficacy is that the drug molecule needs to be stable at physiologic temperature for the duration of therapy. "Also, is the efficacy the same if you deliver the drug at a steady rate over long periods of time compared to peaks and valleys with intermittent dosing?" Ehrlich pondered. "Clinical experiments such as our study and other trials in the field will help provide essential answers."

WATER-FREE SOLUTIONS

The water-free *EyeSol* ocular drug delivery technology from **Novaliq GmbH** (Heidelberg, Germany) is designed to overcome the limitations of water-based ocular therapeutics. "We have taken traditionally poorly soluble or unstable drugs and customized them for high efficacy, bioavailability, stability, safety and comfort," said Oliver Schlüter, managing director of the company.

The enhanced drug-delivery spreading properties support drug distribution on the corneal surface. In addition, EyeSol's low viscosity and low surface tension result in a much smaller droplet size compared to water: roughly 10 microliters compared to between 40 and 50 microliters for a conventional aqueous drop. "Thus, spillover and the immediate loss of the majority of the administered dose are avoided," Schlüter said. "The avoidance of spillover on the bioavailability is a significant delivery advantage."

NovaTears is the first product from Novaliq's EyeSol platform; it is a water-free eye lipid layer stabilizer for evaporative dry eye that effectively stabilizes the lipid layer of the tear film, thereby preventing excessive evaporation. "This ultimately leads to an improvement in signs and symptoms of dry eye," Schlüter said. "Current aqueous artificial tears primarily supplement the water phase of the tear film. The duration of effect is still a subject of investigation; however, there is plenty of data demonstrating that applying eye drops four times a day is effective. Recent data, though, also confirms a long surface retention, indicating that a less frequent regimen may be effective as well."

Results of two prospective noninterventional studies of NovaTears show improvements of signs and symptoms of dry eye disease (DED) in patients suffering from hyperevaporative DED and patients suffering from DED caused by meibomian gland dysfunction, respectively.

NovaTears has been marketed in Europe by **Ursapharm GmbH** since 2015. "To date, we have sold more than one million bottles," Schlüter said. "The product has been proven to be safe and well accepted."

The eye drop is available in multi-dose bottles and neither contains surfactants or preservatives, which are both compound classes that have adverse effects on the ocular surface. "In contrast to other eye drop formulations, NovaTears does not cause blurred vision," Schlüter said.

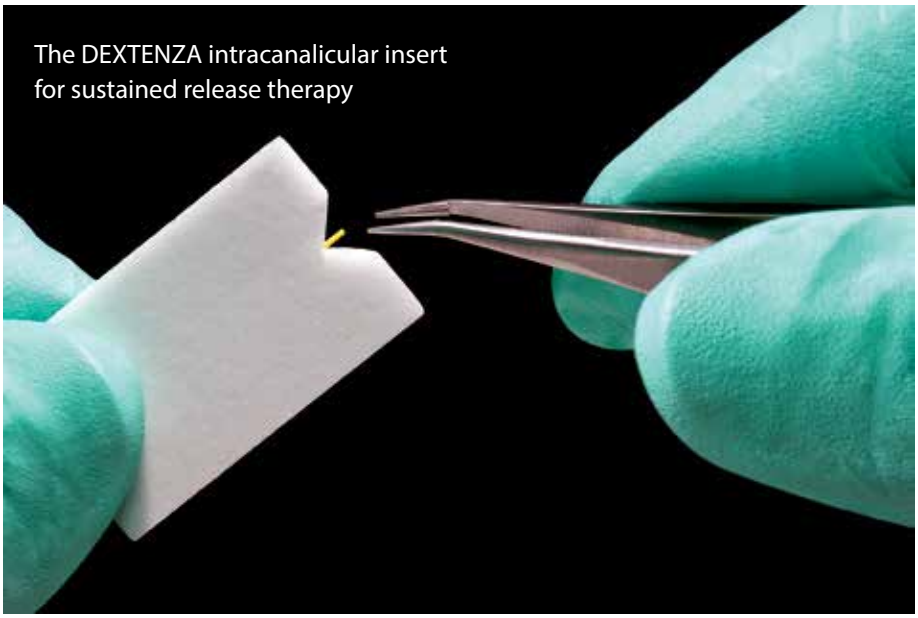
Next year, Novaliq expects to launch in Europe NovaTears + Omega-3, "the first artificial tears containing high concentrated omega-3 of plant origin with high stability at room temperature," Schlüter conveyed.

DRUG INSERT FOR PAIN AND INFLAMMATION

Publicly traded **Ocular Therapeutix Inc.** (Bedford, Mass.) has completed three Phase 3 clinical trials of a sustained-release dexamethasone 0.4 mg insert for treatment of ocular pain and inflammation after ophthalmic surgery, primarily cataract surgery. The intracanalicular insert, *DEXTENZA*, delivers a tapered, preservative-free, 30-day dose of the drug.

The insert, which is 3 mm long, consists of a polyethylene glycol (PEG) hydrogel containing dexamethasone. The insert is formulated as a dried hydrogel rod and is placed

Ocular Therapeutix Inc.'s DEXTENZA



The DEXTENZA intracanalicular insert for sustained release therapy

Source: Ocular Therapeutix Inc.

postoperatively and noninvasively though the punctum (a tear drain on the edge of the eyelid) and into the canaliculus (a small passageway) by a physician using forceps. "In clinical trials, we checked the diameter of the punctum and confirmed adequate punctal diameter, but in clinical practice with nonmedicated plugs, the eye often does not require further dilation," said Scott Corning, vice president of marketing and commercial operations for the company. Insertion takes approximately 10 seconds.

DEXTENZA does not protrude from the punctal opening; however, the product is conjugated with fluorescein for easy detection with a blue light in a dark room or at the slit-lamp with a blue light and a yellow filter. Within 45 to 60 days, the insert degrades and completely resorbs through the nasolacrimal duct.

The Phase 3 trials provide data for the potential use of DEXTENZA for post-surgical ocular pain. If approved for commercial sale, DEXTENZA may become a viable alternative to steroid eye drops, which are associated with patient compliance issues. "In 2016, sales of ophthalmic steroids in the U.S. were roughly $775m, representing about nine million prescriptions," Corning said.

Postsurgical dry eye is a common side effect of ocular surgery, so the fact the punctum remains occluded is a potential ancillary benefit, according to Corning.

A second drug insert from Ocular Therapeutix, also for intracanalicular use, is in clinical development for the treatment of glaucoma. OTX-TP, which is similar in dimension and has the same noninvasive insertion technique as DEXTENZA, provides up to a 3-month release of travoprost, a preservative-free, prostaglandin analog for the treatment of glaucoma and ocular hypertension.

The first of two Phase 3 clinical trials of OTX-TP is currently enrolling, with the second clinical trial initiating later this year. A previous Phase 2 clinical trial showed a lowering of IOP over both a 60- and 90-day period.

Compliance concerns of an eye drop are mitigated with OTX-TP. "In 2016, the prostaglandin analog prescription market for glaucoma was about $1.5 billion a year in the US, with about 18 million prescriptions," Corning says.

The company is also in preclinical development of two sustained-release injections in the posterior segment of the eye to treat such diseases as wet AMD, DME and retinal vein occlusion (RVO). "These depots, one a protein and one a small molecule, would be in lieu of current standard-of-care injections," Corning noted. "They would greatly advance the standard of care by significantly reducing the frequency of monthly or every-other-month injections." For instance, a patient might schedule an injection only once every 4 to 6 months.

The protein injection is in collaboration with **Regeneron Pharmaceuticals Inc**. for a sustained release of its anti-VEGF aflibercept (*Eylea*). The other product, which is being developed internally, is a tyrosine kinase inhibitor (TKI) depot injection. "Our goal is to maintain the same injection technique and gauge needle for both injections as are currently used in clinical practice today," Corning said. "In addition, each drug is encapsulated within our hydrogel for slower release, providing therapeutic tissue concentrations comparable to monthly injections."

GEL-BASED IMPLANTS

ReVana Therapeutics Ltd. was spun out of Queen's University Belfast in the UK in 2014 and in March this year, it took on Michael O'Rourke of Scotia Vision Consultants as CEO. One of the two products in preclinical phase is *OcuLief*, a photo-cross-linking technology. A polymeric gel containing a drug is injected in the eye and then exposed to ultraviolet (UV) light. "The UV light hardens the gel inside the eye," O'Rourke explained. "The hardened gel controls the drug release rate."

The second product, *EyeLief*, is a preformed polymer-based implant with the drug already contained within. Once the implant is injected into the eye, the drug is slowly released.

Both implants have potential for both AMD and glaucoma. "We are looking at the ability to deliver both small molecules for glaucoma and large molecules for AMD," O'Rourke said. Duration of effect could range from 1 month to 1 year. However, clinical studies are likely still two to three years away.

Published online 08/22/17

ESC 2017: Renal-Denervation Redux? Medtronic Plans A New Pivotal Study Following Positive Data

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After several years of second-guessing in the medical community, Medtronic has reported a positive development toward restoring renal denervation's prospects as a promising treatment option for hypertension.

A statistically significant reduction in blood pressure was found from renal denervation in sham-controlled, three-month data from 80 patients presented Aug. 28 at the European Society of Cardiology in Barcelona and published simultaneously in the journal *The Lancet*. The results – partial data from Medtronic's SPYRAL HTN-OFF MED Study – are good enough for the company to announce that it was moving forward with a new pivotal renal denervation study to support device approval in the US, Japan and other regions.

The news comes more than three-and-a-half years after Medtronic announced that its first renal-denervation pivotal study, SYMPLICITY HTN-3, failed to meet its primary endpoint, sending the technique that had generated substantial clinical and market excitement into a period of uncertainty. *(Also see "Renal Denervation Downer: Medtronic's Pivotal Trial Misses Efficacy Endpoint" - Medtech Insight, 10 Jan, 2014.)*

Although SYMPLICITY HTN-3 cast doubt on the efficacy of renal denervation in general, some firms – Medtronic and Boston Scientific, in particular – have continued to develop renal denervation technologies. They point out that SYMPLICITY HTN-3 may have failed to show a benefit for the therapy because there was too much uncontrolled variability in the medication regiments of the patients in the trial.

SPYRAL HTN-OFF MED is part of Medtronic's strategy to better control the variables. It's a sham-controlled pilot study enrolling a total of 353 patients with mild-to-moderate hypertension who are not taking antihypertensive drugs (either they have never, or agreed to go off them for four months) to isolate the procedure's effect on blood pressure reduction.

Among the first 80 patients, those who underwent renal denervation had their office systolic blood pressure decline an average 10 mm Hg, resulting in a 7.7 mm Hg difference with the patients in the sham control arm. Also, diastolic blood pressure declined an average 5.3 mm Hg in the renal denervation group, resulting in a 4.9 mm Hg difference with the sham therapy group.

"These data confirm our long-held belief that the underlying science behind renal denervation is strong, and we are committed to continuing our mission to realize the full potential of this procedure to help address an unmet need for the more than 1 billion people worldwide living with high blood pressure," said Sean Salmon, senior VP and president of Medtronic's Coronary and Structural Heart division. "We intend to continue consulting with our physician advisors and global regulatory authorities about these results so that we can appropriately move forward with a pivotal trial design to ultimately support regulatory approval in the US, Japan and other countries where the technology is not currently available."

Shutterstock: hywards

Medtronic is separately running the SPYRAL HTN-ON MED pilot study to evaluate effect of RDN in patients with uncontrolled hypertension who are still taking their antihypertensive medications. From a commercial standpoint, that data will be more important, underscored Larry Biegelsen, a device market analyst from Wells Fargo.

"If renal denervation were to be approved, its initial clinical use would most likely be as adjunctive therapy for uncontrolled hypertensive patients still on medication," Biegelsen pointed out in an Aug. 28 research note. "We think clinicians will be reluctant (at least early on) to use RDN in newly diagnosed patients or in patients who want to come off their medications."

Still, the initial SPYRAL HTN-OFF MED provides some reason to reconsider the promise of renal denervation. Clinicians will be looking closely to see what happens to the rest of the patients in the study, though. There was a noticeable amount of intra-patient variability in the level of blood pressure reduction observed in the three-month data, Biegelsen noted. In addition, "only about 75% of patients saw a treatment benefit from RDN in the data presented," he said.

Other companies hoping to take advantage of long-term market opportunities in renal denervation may also be buoyed by Medtronic's interim success. Boston Scientific is sponsoring the REDUCE HTN REINFORCE trial with of its *Vessix* renal denervation device, with a similar trial design to SPYRAL HTN OFF-MED. That trial is scheduled to be finished by about next February. *(Also see "Renal Denervation Round 2: Medtronic, Boston Sci Move Ahead With Studies" - Medtech Insight, 18 Feb, 2015.)*

Published online 08/27/17

Siemens Unveils First 7-Tesla MRI Scanner For The Clinic

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Source: Siemens Healtineers

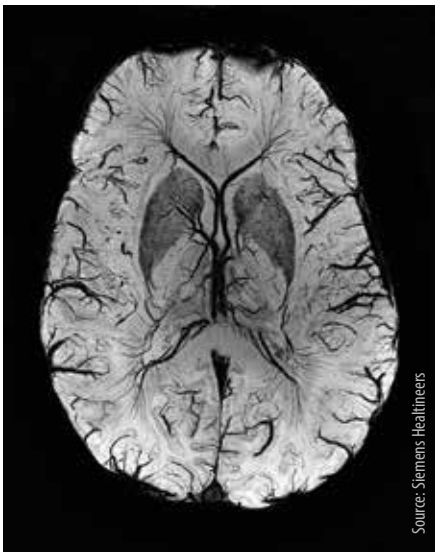
Magnetom Terra MRI Scanner

Siemens Healtineers' *Magnetom Terra* became is the first ultra-high-field magnetic resonance imaging system to be approved for clinical use with the CE mark of the 7- Tesla system, the company announced by the company August 22.

Tesla is the unit of measure for the strength of the magnetic field created by the MRI system. 7T systems have been used in research for about two decades, but this the CE mark means clinicians in Europe can use the 7T system in routine clinical practice to create extremely high-resolution images of neurological and musculoskeletal structures. A 510(k) for Magnetom Terra is pending with the US FDA.

"Having now gained approval for clinical use, we are expanding the scope of diagnostic MRI – 15 years after 3T scanners first became established. With this new clinical field strength, we can achieve a new level of detail in anatomy and function, helping further pave the way for precision medicine," Christoph Zindel, Senior Vice President and General Manager of Magnetic Resonance Imaging at Siemens Healthineers, said in a press release. "I am convinced that Magnetom Terra will help grow the footprint of 7 Tesla in research and clinical application, allowing us to further explore new territories in MRI."

7-Tesla MR Image Of The Brain



Source: Siemens Healtineers

Visualization of very structures is possible with the high resolution of 7T, according to Siemens. This is a susceptibility- weighted image of a healthy brain with minimum intensity projection.

An example ofOne of the 7T system's unique capabilities is its ability to clearer clearly distinguish between white and gray matter in the brains of epilepsy patients, opening-up new diagnostic capabilities, according to Siemens. 7T images of the brains of multiple sclerosis patients could, for the first time, identify lesions in the gray brain matter that cause cognitive impairments.

Magnetom Terra features an actively shielded magnet that is the half as heavy asweight on any other available 7T whole-body shielded magnet available before. The low weight of the system will make it relatively easy to install, and because it runs the same software platform as Siemens Healthineers' 1.5T and 3T scanners, users should be able to learn how to use it quickly, the company says. Magnetom Terra also comes ready with specially optimized applications for 7T imaging to allow easy operation in clinical practice and the exchange of study protocols across other MR systems.

"The combination of a better signal-to-noise ratio, stronger tissue contrast, and greater spatial resolution means that 7T can reveal information that would be invisible at 3T," Siemens says. Until now, 7T has been used for to research into extremely small pathologies and to perform functional imaging of sub-cortical brain activations. Now that the technology will be more w*idespread* and used in clinical practice, it "could be thought of as a MRI microscope that examines the anatomy, function, and metabolism of body tissue," according to Siemens.

The Magnetom Terra's open- system architecture will also be attractive to researchers because it lets them modify the system based on their own needs. Magnetom Terra features Siemens' Dual Mode functionality, which allows users to quickly switch between the clinical protocols and research modes. This makes the 7T system a good platform for translational research, according to the company.

Published online 08/23/17

Medtronic's Q1 Top Line Tumbles Due To Global IT Crash

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Medtronic PLC fiscal first quarter revenue took a hit from a global computer crash that shut down the company's systems for global ordering, fulfillment and manufacturing for a week in June.

The medtech giant reported Aug. 22 that its fiscal first-quarter worldwide revenue was $7.4bn, an increase of 4% on a constant currency basis year-over-year, but lower than analyst consensus estimates of $7.45bn. Medtronic said the approximate $30m top-line shortfall (vs. recently updated guidance) was due to an IT disruption, which impacted the company's visibility through quarter-end.

Last month, Medtronic updated its FYQ1 sales guidance to the lower end of the 4-5% range but remained confident the crash would not impact its revenue growth projections for the first quarter.

"When we updated our guidance in July, we expected our revenue would be slightly higher, but the IT disruption caused a unique dynamic, affecting our visibility through quarter-end as we worked to clear the order backlog, including higher-than-expected sensor demand in Diabetes," Medtronic CFO Karen Parkhill told investors during the company's first-quarter earnings conference call.

An independent analysis conducted by Ernst & Young in partnership with Medtronic's technology experts and vendor partners concluded that the root cause of the crash was "inadvertent human error," which caused a misconfiguration within certain data storage systems and resulted in its IT system becoming inoperable.

Q1 results showed sales in Medtronic's diabetes product revenues dropped by 1% year-over-year to $449m, due to a supply shortfall of the company's glucose monitor sensors. The company said it had experienced strong global demand for its new sensor-augmented insulin pump systems, but was being temporarily affected by the previously disclosed limited supply of continuous glucose monitor sensors.

Last month, Medtronic launched the first hybrid closed loop system, the *MiniMed 670G*, in the US which the company said led to increased demand and adoption of its sensor-augmented insulin pumps. CEO Omar Ishrak told analysts during the earnings call that additional demand had resulted in fulfillment prioritization to the existing installed based, including MiniMed 670G Priority Access Program customers, affecting sales of sensor-augmented pumps to new customers in the near-term. Strong customer enrollment in its Priority Access Program also temporarily affected revenue growth.

"The increased demand is largely for the new, highly accurate generation of sensors, the enhanced Enlite in international markets, and the Guardian Sensor 3 in the US and has temporarily outstripped our production capacity," said Ishrak. "We accelerated plans to increase sensor production capacity last year, but these lines are not expected to be ready for commercial production until our fourth quarter; at which time, we expect to have the capacity needed to meet the rapidly growing sensor demand."

Medtronic's Cardiac and Vascular Group (CVG) first quarter revenue of $2.6bn increased 6% on a constant currency basis, with sales of transcatheter valves, AF ablation, LVADs, transcatheter pacing systems, insertable diagnostics, atherectomy and drug-coated balloons, all contributing to the growth.

In TAVR, the company delivered growth in the high-30s in both the US and international markets. Ishrak said the company expected the global rollout of its recently FDA-approved *Evolut PRO* transcatheter valve to drive continued growth in the sector.

Medtronic also saw significant gains in its Brain Therapies division. Revenue of $522m grew 7%, driven by high-teens growth in Neurovascular and high-single digit growth in Neurosurgery. The division received a boost from the recently launched *StealthStation S8* surgical navigation system and growth of the *Solitaire* family of revascularization devices for acute ischemic stroke.

Overall, Medtronic affirmed sales guidance of 4-5% comparable ex-FX growth and FY 2018 non- GAAP EPS growth of 9-10% ex-FX.

Jefferies analyst Raj Denhoy noted that Medtronic's first-quarter growth was "disappointing," and pegged the company's organic growth in FY18 at 3.6%, lower than Medtronic's sales guidance. Commenting on Medtronic's sensor supply shortfall, Denhoy wrote: "The poor manufacturing planning and execution makes the ultimate impact of what was once a long head start in automated insulin delivery less meaningful for Medtronic and the companies coming behind it."

Medtronic's FY2018 First Quarter Revenues

DIVISION	NET REVENUE (IN $ MILLIONS)	% YEAR-OVER-YEAR GROWTH OR (DECLINE) IN CONSTANT CURRENCY
Cardiac & Vascular Group	**2,646**	**+6**
Cardiac Rhythm & Heart Failure	1,390	+5
Coronary & Structural Heart	817	+8
Aortic & Peripheral Vascular	439	+5
Minimally Invasive Therapies Group	**2,486**	**+3**
Surgical Solutions	1,399	+4
Patient Monitoring & Recovery	1,087	+1
Restorative Therapies Group	**1,809**	**+2**
Spine	649	+1
Brain Therapies	522	+7
Specialty Therapies	369	+4
Diabetes Group	**449**	**-1**
TOTAL	**7,390**	**+4**

Published online 08/23/17

Carl Zeiss Meditec Sees Data Management Potential In Cataract Surgery

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Carl Zeiss Meditec AG has acquired the privately held developer of a new intelligent cloud-based platform for collating patient data from electronic medical records and diagnostic devices that would help ophthalmic surgeons with the planning of cataract surgery for each patient and the management of post-operative care.

Veracity Innovations LLC, which was bought for an undisclosed sum, unveiled the Veracity platform at the American Society of Cataract and Refractive Surgery in May. It is designed to present "the most relevant and critical data that is needed at each step" across the whole patient care pathway, from consultation right through to the post-operative process.

One similar data management product in Zeiss's portfolio is Forum, which connects diagnostics devices, integrates the data from multiple modalities and delivers the required information to the doctor's office or in the operating room. But while Forum is a broader platform – segmented into different Clinical Workplace apps like Glaucoma Workplace – Veracity is focused on cataract surgery.

"[With Forum,] Zeiss already provides advanced digital solutions that support doctors in their clinical decisions and provide for efficient data management…Now we are complementing this with the Veracity platform – a simple, cloud-based solution that provides doctors, and their teams, exactly the information they need at each step in the clinical process so they can work more efficiently, mitigate risks, and achieve the very best possible outcomes for their patients," says Jim Mazzo, Global President Ophthalmic Devices at Carl Zeiss Meditec.

Ophthalmic devices account for the much larger of Carl Zeiss Meditec's two strategic business unit, the other unit being microsurgery. Earlier in August, the company reported an 8.3% year-over-year increase in revenue, at €864.7m, for the first nine months of 2016/2017. This was driven by the 9.2% growth in revenue for ophthalmic devices, at €639.9m. Microsurgery saw revenue grow 5.6% to €224.8m.

Published online 08/22/17

Dexcom Looks To Expansion, Operational Efficiency For Rapid Growth

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It's been a period of rapid growth for continuous glucose monitor maker Dexcom. Earlier this year, the San Diego-based company's CGMs were the first to be made eligible by the US Centers for Medicaid and Medicare Services for reimbursement *(Also see "Dexcom First To CGM Reimbursement Finish Line" - Medtech Insight, 17 Jan, 2017.)* and in the first six months of 2017, the company's revenue grew 23%.

"When I started at Dexcom six years ago our revenues were just over $60m in my first year and based on Wall Street estimates it's going to be $700m-plus in 2017," Dexcom CEO, Kevin Sayer told *Medtech Insight*.

"Our compounding growth rate over the past several years has been around 50%. But despite this rapid growth, we need to focus inward on doing things more efficiently over time. We don't ever want to kill our growth rate and generating positive cash flow. One of the key words in our growth over the next several years is expansion, scaling up, getting into new markets and serving our current markets better."

Dexcom believe the next big opportunity is taking its technology to the Type 2 diabetes market. The company is championing a 'CGM first' message to promote CGMs as the primary tool to manage diabetes. While the benefits of Type 1 diabetes patients using a CGM are clear cut, the clinical community has been more skeptical of its use for Type 2 diabetics. However, recent studies have indicated continuous glucose monitoring could positively aid the management of Type 2 diabetes for patients.

"What we've learned in the studies we've done so far is that people with Type 2 diabetes typically get very little coaching as far as what to do to manage their condition so our products for Type 2 will be both an educational and diagnostic tool. There are millions more people with Type 2 diabetes, than Type 1 so we see this large market as a huge opportunity to help and one that will ultimately reduce healthcare costs."

Stepping in to oversee Dexcom's commercial strategy is former CFO at spine specialist NuVasive, Quentin Blackford. The new CFO will join the management team from September, replacing Jess Roper who retired in March. "My expectation for Quentin is to immediately meld and become part of our team and help us identify more efficient commercial strategies to help us grow and really get involved at looking at our relationships with those who pay for our technology," said Sayer. "We want him to look at ways to streamline the business and help us do better on the commercial side by evaluating the possible returns on alternative markets that we can go into."

"We're very public about taking our technology to Type 2 diabetes but we need to make sure that the steps we take lead to a financial home run down the road," said Sayer. "Quentin will help us really ramp up Dexcom's financial discipline because while we've grown very quickly on the revenue side, there's a time in every company's history where they transition to be more earnings focused, and that's now where we're at."

Expanding into additional geographical markets will also be key to Dexcom's expansion, with the company seeing the most potential in in Europe. "We got very strong reimbursement in Germany this year and we've had a hard time quite frankly keeping up with the growth," said Sayer. Dexcom will be doubling the size of its sales force in Germany over the next several months to grow its market share further. "We've had great success in Europe because of the strength of our product. The European community is very much enjoying the connectivity and the technology sharing data that our products provide."

Sayer said Dexcom is looking for stronger reimbursement models to solidify business in countries such as Italy and the UK, where coverage is currently sporadic. "We would like to even the playing field there and get better increased coverage. We're also starting some efforts in France and in Asia, we hope to get our first approval for a product in Japan before the end of the year." But to really capture the Asian markets, Dexcom is masterminding a bigger plan with the Google Life Sciences arm, Verily.

The two companies are currently developing a miniature-sized CGM that requires no calibration and can be marketed to people with both type 1 and type 2 diabetes. Sayer said: "We're giving some thought to Asian markets but the product we develop with Verily is what is going to very attractive to those markets."

Published online 08/25/17

World of Change Coming For Device Manufacturers: Developments In FDA And International Inspections

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As medical technologies have become increasingly sophisticated and varied, US FDA has been confronted with the need for a more specialized inspectorate. Similarly, the increasingly globalized nature of medical device production has stretched FDA's inspection resources, leading the agency to explore ways of working collaboratively with other regulators around the world. In turn, device-makers have had to grapple with FDA's changing expectations, the potential for varying standards imposed by different regulators across the globe, and a lack of clarity as to FDA's specific expectations for addressing inspection observations.

FDA and Congress have recently taken significant steps to improve regulatory efficiency and predictability in the inspection of medical device facilities. Device-makers will need to adjust their practices to take advantage of three important initiatives that have advanced in recent months:

- FDA has implemented the Program Alignment initiative to increase the specialization of investigators and their supervisors.
- Congress enacted the FDA Reauthorization Act of 2017 (FDARA), which reforms FDA's inspections practices for medical device establishments.
- FDA and other regulators have made significant progress toward implementing the Medical Device Single Audit Program (MDSAP), which allows multiple countries' regulators to rely on a single inspection.

These changes, if implemented effectively, offer device-makers opportunities to streamline and enhance their compliance and quality programs.

PROGRAM ALIGNMENT

On May 15, FDA implemented Program Alignment in its Office of Regulatory Affairs (ORA), which, among other functions, conducts inspections of medical device manufacturers. *(Also see "'Program Alignment' Falls Into Place: Everything You Need To Know About US FDA's New Inspectional Approach" - Medtech Insight, 8 May, 2017.)*

Program Alignment is a reorganization of the 5,000-person ORA that shifts management of operations, including inspections, from one that is based on geography to one based on areas of regulatory expertise. Investigators and their supervisors will be now be housed in one of seven offices: Medical Devices and Radiological Health; Biologics; Import Operations; Pharmaceuticals; Bioresearch Monitoring, which oversees clinical trials; Human and Animal Food; and Tobacco. Prior to Program Alignment, ORA assigned investigators to geographic regions, and investigators would generally oversee FDA-regulated facilities within that region, regardless of product type.

Although most FDA investigators were already specialized by commodity type, Program Alignment will ensure that *all* FDA investigators are specialized, making it easier for investigators to remain up to date on medical device technology and policy while not having also to focus on, say, food safety policy. It will

also ensure that the supervisors who help decide which facilities to inspect and review recommendations for compliance actions are medical-device specialists. Prior to Program Alignment, these supervisors had responsibility for all commodities in their geographic area, regardless of their own expertise. Because investigators and supervisors are now responsible for only one commodity, they will have the opportunity to work more closely with FDA's Center for Devices and Radiological Health.

A closer working relationship between specialized ORA supervisors and investigators and CDRH experts should improve predictability and consistency. It remains to be seen how ORA will implement the device-focused investigators across a wide array of device technologies: Will there be subspecialists focused on diagnostics, for example, or on software-only medical devices?

For the moment, when responding to inspections or engaging with FDA, it is important for firms to understand the roles that the relevant officials will play in the newly reorganized ORA, and to anticipate some transition in the investigators and supervisors with whom they typically engage. Over the longer term, device establishments should view Program Alignment as an opportunity to develop a more cooperative relationship with investigators who will be increasingly dedicated to understanding their particular technologies.

FDA REAUTHORIZATION ACT

On August 18, President Trump signed FDARA, which reauthorizes user fees for pharmaceuticals and medical devices for five years. *(Also see "MDUFA IV (And More) Is Law: Trump Signs A Health-Care Bill" - Medtech Insight, 18 Aug, 2017.)* FDARA contains provisions that touch many aspects of device regulation. One key focus of FDARA's device provisions is improving efficiency and predictability with respect to inspections and resulting inspection observations (known as "483s," after the form on which they are conveyed).

Under FDARA, FDA must implement a risk-based medical device inspection schedule. The inspection schedule will be arranged based on factors such as the nature of the device, compliance history, its past inspection frequency, and whether the establishment participates in an international audit program (such as MDSAP). Making inspections formally risk-based will reduce the resource drain from inspections that have limited public health utility. FDARA's nod to international audit programs and discouraging duplicative inspections acknowledges the resource challenges associated with globalization.

FDARA also requires FDA to improve the transparency and predictability of inspections, expand opportunities for communications, and facilitate the resolution of inspection observations. The process improvements are designed to address an industry concern that FDA's inspections decisions are sometimes unpredictable and opaque. In particular, FDARA directs FDA to announce device inspections in advance, with estimates of the timeframe for the inspection and an opportunity for advance communications with the inspection team concerning topics such as the establishment's typical hours of operation and the types of records to be reviewed. In addition, FDA is directed to develop policies providing for inspections to take place on consecutive days (rather than sporadically over a period of time) and to develop standardized communications templates to facilitate more consistent information exchange. FDARA establishes deadlines for FDA to publish draft and final guidances that implement these changes.

Even more significantly, FDARA creates an opportunity for device establishments to request informal feedback on their proposed corrective actions to address certain deficiencies identified during an inspection. This provision addresses concerns by device sponsors that they often undertake costly or complex corrective actions without any clear signal from FDA that their actions will fully address the agency's concerns. Under FDARA, if an FDA inspections report contains observations and related corrective actions that implicate a public health priority or an emerging safety issue, or would involve systemic or major undertakings by the establishment, then FDA must respond to a request for "nonbinding" feedback on the proposed actions within 45 days.

These changes create a new paradigm for device inspections, which, if implemented constructively, will complement and enhance FDA's Program Alignment initiative. For device establishments, these changes may dictate corresponding revisions to their internal procedures governing the conduct of inspections and responses to inspection observations. To take advantage of these changes, device establishments should work proactively to leverage these enhanced opportunities for open communication with FDA before, during, and after an inspection. More importantly, by providing for advance communications about corrective actions between the establishment and FDA personnel—rather than FDA only assessing changes retroactively—FDARA has improved the likelihood that establishments will be able to satisfy FDA's expectations as quickly as possible.

MEDICAL DEVICE SINGLE AUDIT PROGRAM

The medical device market has become increasingly global. FDA estimates that imported medical devices constitute 35 percent of the US market. FDA and other regulators must increasingly conduct oversight of products manufactured or developed outside their borders. The need to conduct foreign inspections creates a resource challenge for FDA because foreign inspections incur additional travel and planning costs. Also, if foreign regulators do not coordinate their activities, a firm may be inspected repeatedly, in a short time span, by different regulators, with inconsistent results. Conversely, other firms might be inspected too infrequently, due to lack of resources—potentially leaving safety risks unidentified.

MDSAP is designed to address these challenges. *(Also see "More Manufacturers Sign Up For Single Audits As MDSAP Becomes Operational" - Medtech Insight, 16 Feb, 2017.)* MDSAP allows a "recognized Auditing Organization" (an entity authorized to audit under MDSAP requirements) to conduct a single, standardized regulatory audit of a medical device manufacturer. The five countries that currently participate in MDSAP (Australia, Brazil, Canada, the US, and Japan) then rely on this audit. The European Union is an Official Observer to the MDSAP's governing board, the Regulatory Authority Council, and may choose to join MDSAP in the future. Each of the five MDSAP regulators uses the audits slightly

differently. FDA will accept an MDSAP audit report as a substitute for many FDA routine inspections, but not as a substitute for "for cause" or "compliance follow-up" inspections. Notably, under the FDARA reforms, MDSAP participation will also result in lowering an establishment's risk profile. On June 29, the MDSAP Regulatory Authority Council issued a report concluding that a pilot of MDSAP was successful, signaling that the program will continue.

MDSAP participants will be audited on a three-year certification cycle, with one audit occurring each year. The first-year audit, called an Initial Certification Audit, is a complete audit of a medical device manufacturer's quality management system (QMS). This audit determines if MDSAP documentation and regulatory requirements have been met, and evaluates technology used by a manufacturer. The Initial Certification Audit is followed by two yearly partial Surveillance Audits conducted once per year for two years. The cycle then recommences with a Recertification Audit. Other audits by regulatory agencies, including "for cause" inspections, may still occur.

The MDSAP audit process has several advantages, for firms and FDA. MDSAP allows the regulatory assessment process among multiple governments to be serviced by one auditor, meaning there is less business disruption and more consistency. MDSAP audits are announced, scheduled by the Auditing Organization with the manufacturer, and assigned a pre-established duration, minimizing business disruptions to the device company.

Published online 08/25/17

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FDA Assembling Advisors To Discuss Pediatric HDE Products

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FDA's Pediatric Advisory Committee (PAC) is scheduled to meet for two days in mid-September to discuss a range of products, including four devices with humanitarian device exemptions (HDE) for use in kids.

In an Aug. 22 Federal Register notice, FDA says it is convening its panel of pediatric experts in Gaithersburg, Md., on Sept. 11 and 12. The first day will be dedicated to discussion on prescribing children opioid products containing hydrocodone or codeine to treat coughs.

On the second day of the meeting, the agency plans to talk about the HDE products, some of which have been in use now for more than a decade. The PAC is statutorily mandated to perform pediatric-focused safety reviews for devices, drugs and biologics periodically. *(Also see "Safety Of Five Devices To Be Reviewed At FDA Pediatric Panel Meeting" - Medtech Insight, 17 Aug, 2016.)*

Among the pediatric devices to be reviewed is **Medtronic PLC**'s *Contegra Pulmonary Valved Conduit*, a pulmonic valved conduit to correct or reconstruct the right ventricular outflow tract (RVOT), intended to treat certain congenital heart malformations. The device has been available under an HDE since 2003. *(Also see "Medtronic Contegra" - Medtech Insight, 1 Dec, 2003.)*

Medtronic PLC's *Enterra Therapy System* will also be discussed. An intestinal stimulator, the device has been available under HDE since 2000. The gastric electrical stimulation (GES) system is indicated to treat chronic, intractable (drug refractory) nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology. *(Also see "FDA gives HDE (humanitarian device exemption) approval for gastric stimulation system" - Medtech Insight, 17 Apr, 2000.)*

Third on the list, FDA advisors will discuss Plexision's *Pleximmune* test. FDA approved an HDE for the device in 2014. It is a qualitative prognostic test intended for use in patients who younger than 21 and are about to undergo liver or small bowel transplantation. The test is meant to help physicians figure out the risk of organ rejection in conjunction with biopsies, standard clinical assessments and other laboratory information.

Finally, the panel will also discuss Elana's *Elana Surgical Kit*, which gained HDE status in 2011. When connected to the **Spectranetics Corp.'s** *Xenon-Chloride Laser Model CVX-300*, it is indicated to create incisions in the artery wall during an intracranial vascular bypass procedure for patients 13 and older with an aneurysm or a skull-base tumor affecting a large intracranial artery. *(Also see "New Products In Brief" - Medtech Insight, 21 Mar, 2011.)*

Each of these devices were reviewed last year by FDA's committee. The only device not up for re-review this year is **Berlin Heart AG**'s *Excor* pediatric ventricular assist device, which gained PMA approval in June.

FDA declined to comment on what specific questions the pediatric advisory committee will address, but the agency does plan to submit briefing documents for the advisors at least two days before they meet.

Stakeholders interested in submitting comments to the advisory committee can do so on Regulations.gov, under docket no. FDA-2017-N-4885. Comments submitted by Aug. 28 will be reviewed by the committee but those received after will still be taken into consideration by FDA.

Published online 08/22/17

FDA Pediatric Device Approval Rate Stays Level

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Less than a month after US FDA sent Congress a report on the number of pediatric device indications approved in FY2015, the agency has followed up with another report to lawmakers reporting no change in the proportion of such approvals in FY2016.

FDA is mandated to present data on pediatric device approvals to lawmakers annually. Following its report to Congress last month providing data from FY2015, the agency has caught up on its mandate by releasing its FY2016 data in a report dated Aug. 1, 2017. *(Also see "Snapshot: US Pediatric Device Approvals Stay Steady, Despite Overall FDA Surge" - Medtech Insight, 27 Jul, 2017.)*

While the number of pediatric device approvals via original PMAs, panel-track supplements and humanitarian device exemptions (HDEs) is up from FY 2015, total approvals also increased, such that the proportion of approvals with pediatric indications remained unchanged, according to the report.

FDA says it approved 71 devices in 2016, which is up from 61 approvals from the previous year; a 16% increase. Similarly, of those devices, 13 included pediatric indications, which is up from 11 such approvals the previous year; an 18% increase from FY2015. The proportion of pediatric devices approved by FDA of total approvals has stayed the same at 18%.

> Only two of the 13 pediatric devices approved were exclusively for children and, thus, were statutorily exempt from user fees.

Breaking down the numbers of the 71 total devices approved, 68 were PMAs and three were HDEs. All 13 pediatric devices approved last year were PMAs. FDA also notes that 62 of the FY 2016 PMAs and all three HDEs addressed indications that affect children, though not all were approved to treat children.

Only two of the 13 pediatric devices approved were exclusively for children and, thus, were statutorily exempt from user fees.

The median review time for pediatric devices approved in FY2016 was 180 FDA days and 267 total elapsed review days.

Since FDA started tracking in FY 2008, the highest proportion of pediatric devices approved was in FY2010. That year, the agency approved eight devices with pediatric indications of a total 20 devices approved, which means 40% of devices approved were for children.

Published online 08/25/17

Changes Coming Next Month To US FDA Web-Based Device Export Tracker

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US FDA says it is updating the format of the CDRH Export Certification and Tracking System (CECATS) next month.

"Effective September 25, 2017, CECATS is changing to a new format, which will include the latest phase in a series of ongoing enhancements to the system," FDA said.

The agency plans to host a one-and-a-half-hour webinar on Sept. 19 to outline for manufacturers and exporters of devices the significant changes coming to the online export document system.

Besides walking viewers through the system and its changes, the agency also plans to do a live demonstration of the updated site during the webinar.

The agency first launched CECATS in 2012 to allow manufacturers and exporters an electronic means of processing export certificates. The system is voluntary and meant to reduce paperwork; users are still able to send the agency paper submissions. *(Also see "Electronic system for processing medtech export documents goes live in US" - Medtech Insight, 21 Dec, 2012.)*

FDA made a major upgrade to CECATS in 2014. At the time, the agency also said it would expand the system's capability in early 2015 to accommodate the electronic submission of requests related to non-clinical research-use-only certificates, export permit letters and simple notifications. *(Also see "US FDA stops notarizing device export certificates" - Medtech Insight, 10 Mar, 2014.)*

The agency says those interested in joining the Sept. 19 webinar do not have to register, but it is asking participants to let them know if they plan to attend via a SurveyMonkey poll by Sept. 1.

Published online 08/23/17

Industry Supports US FDA Conformity Assessment Concept, But Questions Abound

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US FDA's plan to allow third-party certified device testing labs, instead of the agency, to sign off on a device firm's conformance to consensus standards should work if it's properly implemented, manufacturers say, but some stakeholders worry that currently recognized consensus standards may not be sufficient to support an FDA pilot.

FDA committed to establishing an Accreditation Scheme for Conformity Assessment (ASCA) in the agency's MDUFA IV user-fee commitment letter. MDUFA IV was formally enacted into law Aug. 18 as part of the FDA Reauthorization Act. *(Also see "US FDA Seeks Input On Standing Up Conformity Assessment Pilot" - Medtech Insight, 17 May, 2017.)*

Under ASCAFDA would accredit third parties to certify that test labs can evaluate whether medical devices meet international consensus standards. The agency would then rely on the reports from the certified labs in its pre-market review of sponsor submissions, rather than staging its own assessment. *(Also see "MDUFA IV (And More) Is Law: Trump Signs A Health-Care Bill" - Medtech Insight, 18 Aug, 2017.)*

Supporters say ASCA would allow medical devices to reach market more quickly. The agency asked stakeholders for comments on a proposed ASCA pilot program in May. The 29 comments received by the June 30 deadline generally back the concept, but questions circulated about how it would work in practice. "The current recognized voluntary consensus standards lack clear definition relating to the established/acceptable acceptance criteria, applicability, and sample sizes," **Smith & Nephew PLC** Orthopedics said in a comment. The firm suggested that FDA consider including in the pilot additional standards that are commonly used by the industry, but aren't yet recognized by FDA.

> "The current recognized voluntary consensus standards lack clear definition relating to the established/acceptable acceptance criteria, applicability, and sample sizes," Smith & Nephew commented to FDA.

Several groups specifically recommended that FDA recognize the ISO 17025 standard on the competence and calibration of testing laboratories as a core component of the pilot program.

"Recognition of ISO 17025 would likely help propel the success of the ASCA program and help harmonize the program globally, even if this would require updates to the ISO 17025 standard and/or its accreditation scheme," **Cook Group Inc.** stated. The diversified device manufacturer further suggested that FDA should recognize as many device-specific standards as possible for the purposes of the pilot. But Cook conceded there might be some challenges because "many medical device standards also do not have complete, detailed, fully executable methods."

Cook highlighted another challenge – the lack of standards for some novel devices. "Would the program allow for accreditation of non-standardized test methods that [are] developed and validated by the test lab, would that differ from the accreditation of standardized tests, and what would be the impact?" Cook asked.

Philips Healthcare, meanwhile, said the pilot should be limited to standards with clear pass-or-fail criteria that do not involve "qualitative" metrics.

Trade association AdvaMed joined manufacturers in pressing FDA to rely on testing-lab certification of applicable standards based solely on a declaration of conformity. "We seek very few, if any, additional information requests related to accredited reports/certifications and/or conformance to the cited standard," AdvaMed said.

Product types suggested for participation in the pilot included infusion sets, catheters, and hypodermic needles and syringes.

FDA also asked stakeholders to outline standards by which the success of the pilot program could be judged. The industry BRIDGE Coalition (formerly known as the 510(k) Coalition) offered an extensive list of factors on which success could be judged, including: that a significant portion of industry use the program; duplicative review by FDA be avoided; and that the pilot program demonstrate that accreditors are competent to judge acceptable vs. non-acceptable deviations.

Most companies said they'd need to know more specifics about the pilot program before agreeing to participate. Philips, for example, said its final decision would be "based on the specific standards defined by the FDA for the pilot, as well as test laboratory accreditation capabilities."

As a next step, the MDUFA IV commitment letter requires that FDA discuss the planned pilot program in a public workshop and hold education sessions about it by the end of FY 2018, and the agency has further said that it will issue a draft guidance by FY 2019 and initiate the pilot program by the end of FY 2020.

Published online 08/28/17

US FDA Fees To Spike In FY 2018, But Small Firms Get Breaks

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US medical device user fee rates are increasing in FY 2018, in some cases significantly, under the newly reauthorized MDUFA IV, but small businesses are given more cushion.

On Aug. 28, US FDA released its final medical device user fee schedule for FY 2018, which begins in October. The rates are based on the MDUFA IV agreement reached between the agency and industry that will raise about $1bn over five years. It was enacted into law as part of the FDA Reauthorization Act earlier this month. *(Also see "Device Week, Aug. 24, 2017: FDA Reauthorization Act Realities" - Medtech Insight, 24 Aug, 2017.)*

While previously released fee amounts were base values, the final rates are adjusted for inflation, and, as with prior user-fee programs, will be discounted for qualifying small businesses.

According to the latest adjusted numbers, 510(k)s, by far the most frequent type of pre-market submission, will see a substantial fee increase, up 124%, from $4,690 in FY 2017 to $10,542 in FY 2018. But, due to an adjustment in how the small-business discount is calculated for 510(k)s, companies reporting revenue of $100m or less will only pay $2,636, up only 12% from FY 2017. (*See table, "User Fee Rates: FY 2018 v. FY 2017"*)

Year-to-year fee-rate increases are accentuated because rates dropped in FY 2017 compared to the prior year due to an over-collection adjustment. *(Also see "US Device User-Fee Rates Will Drop About 10.3% In Fiscal 2017" - Medtech Insight, 1 Aug, 2016.)*

Fees for most other submission types, including PMAs and PMA supplements, classification requests and annual reports, will go up by about 32% in FY 2018, for both the standard and small-business fee. The establishment registration fee will increase by 37% to $4,631.

The other noteworthy change for FY 2018 is the first-time addition of a user fee for *de novo* submissions. *De novo* applications will cost $93,017 for typical businesses and $23,254 for small businesses in FY 2018.

User Fee Rates: FY2018 v. FY2017

STANDARD FEES

FEE TYPE	FY 2017 - STANDARD FEE	FY 2018 - STANDARD	PERCENT INCREASE
510(k)	$4,690	$10,542	124%
De Novo	$0	$93,017	N/A
Original PMA or BLA	$234,495	$310,058	32%
Panel-Track Supplement	$175,871	$232,544	32%
180-Day Supplement	$35,174	$46,509	32%
Real-Time Supplement	$16,415	$21,704	32%
30-Day Notice	$3,752	$4,961	32%
513(g) request for classification	$3,166	$4,186	32%
Periodic reporting on class III devices	$8,207	$10,852	32%
Establishment registration fee	$3,382	$4,631	37%

SMALL-BUSINESS FEES

FEE TYPE	FY 2017 - SMALL BUSINESS	FY 2018 - SMALL BUSINESS	PERCENT INCREASE
510(k)	$2,345	$2,636	12%
De Novo	$0	$23,254	N/A
Panel-Track Supplement	$43,968	$58,156	32%
180-Day Supplement	$8,794	$11,627	32%
Real-Time Supplement	$4,104	$5,426	32%
30-Day Notice	$1,876	$2,481	32%
513(g) request for classification	$1,583	$2,093	32%
PMA annual report	$2,052	$2,713	32%
Establishment registration fee	$3,382	$4,631	37%

SMALL-BUSINESS GUIDANCE

In conjunction with the fee schedule, FDA issued its annual final guidance on "FY 2018 Medical Device User Fee Small Business Qualification and Certification." The document details the MDUFA IV definition of a small business that qualifies for the discounted fee rates – those with annual revenue of no more than $100 million. The guidance also clarifies that in cases where the business rakes in no more than $30 million annually, the company could be eligible for a free pre-market application for their first submission.

The guidance elaborates how FDA determines a company's revenue, whether it is based in the US or abroad.

The guidance also describes potential loopholes that companies may want to use to show they are a small business when in fact they are affiliated with another manufacturer whose combined sales may exceed the $100 million threshold. In such cases, the company would still have to pay the standard user fee rate for a pre-market application.

Companies that are certified by FDA as a small business will maintain that status until September 2018 after which they need to re-apply for the status with the agency.

FDA also states that small companies who only plan on paying for the establishment registration fee in FY 2018, but not any other submissions, will not benefit by also submitting an FY 2018 Small Business Qualification and Certification request because there is no small-business discount for the registration fee. In fact, the agency is asking such small businesses not to submit the form.

In the guidance, FDA also reminds companies it will not charge user fees for 510(k)s submitted to the agency on behalf of an FDA-accredited third-party reviewer. Under the user-fee agreement, FDA has gained additional statutory authority to expand use of the third-party 510(k) program.

Published online 08/28/17

Former FBI Cyber Chief Urges More Proactive Approach to Cybersecurity

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The device and drug industries need to take a more aggressive approach to countering cybersecurity threats, says Jerry Bessette, associate director of Navigant Consulting and former chief of FBI's cyber operations section. The risks are growing and these industries cannot afford to sit back and wait for more such attacks, warned during an Aug. 17 webinar sponsored by Xavier University.

Bessette discussed the industries' readiness to handle cyberattacks, and shared examples of recent hacking events that expose vulnerabilities, and strategies to address the problems.

Bessette said the health-care industry is "lagging behind" other sectors in cybersecurity readiness, yet it is increasingly vulnerable to attacks. He said that "the risks of cyberattacks is growing as the technology of these products advance." *(Also see "Hack Attack: Biopharma Cyber Chiefs Fight Back" - Medtech Insight, 29 Jun, 2017.)*

Devices such as insulin pumps, heart monitors, X-ray systems and communication systems are particularly vulnerable to attack, he said. Hackers can access these systems because of poor cybersecurity monitoring and a lack of cohesive cybersecurity policies.

Hackers can easily find and access device systems using *Shodan*, a search engine for internet-connected devices, said Bessette. A recent survey found that 36,000 health-care devices can be easily discovered on this search engine. Bessette said that "people can look around and see that these devices are speaking." The survey was published by Trend Micro, a cybersecurity solutions company.

Trend Micro also found that a "nontrivial" proportion of health-care systems still use outdated operating systems that no longer receive security updates. This makes them more vulnerable to cyberattacks and provides an entry point for hackers to steal sensitive medical records. *(Also see "Security Firm Confirms 'Petya' Has Affected Medical Devices" - Medtech Insight, 4 Jul, 2017.)*

Hackers can also access pharmacy dispensing systems in hospitals or long-term care facilities, which can result in too much or too little of a drug being dispensed. "This is a concern," he said.

Yet the irony is that device-makers know their products are vulnerable to attacks. A poll of 500 device firms found that two thirds of them believe there will be a major cyberattack in the device industry in the next year.

Bessette said the pharmaceutical industry is also an attractive target for cyberattacks. If R&D units at companies, which hold proprietary material on new drugs, are hacked, a manufacturer can lose years of intellectual property protection.

In response, insurance companies are adjusting their offerings, with some insurers providing new cybersecurity-focused products for device manufacturers and others in the health-care industry to protect companies in the event of a malicious hack or cyber vulnerability. *(Also see "Cyber Insurance Offerings Growing In Response To New Threats" - Medtech Insight, 28 Jul, 2017.)*

SOME RECENT CASES

Bessette described how recent cyberattacks have exposed existing vulnerabilities. He cited:

- A recent investigation of implantable cardioverter defibrillators by British and Belgium researchers, who found security flaws in the proprietary communication protocols on 10 different types of ICDs on the market.
- A hospital in Miami that was hit by data breaches after its medical devices were infected with malware, which entered the network through a device. This security breach allowed hackers to move laterally within the health-care network to steal proprietary information from other devices. The affected devices included a blood gas analyzer, a picture archive, communications systems and an X-ray system – all infiltrated with malware.
- Bayer's confirmation that its power-injector medical systems used in US hospitals to improve imaging of MRIs had been attacked by ransomware called "WannaCry." The ransomware targeted older Windows versions that had not been updated with updated software patches. *(Also see "WannaCry Cybersecurity Alert Shows Medtech Software Must Look Beyond Quick Fixes" - Medtech Insight, 19 May, 2017.)*
- A cyberattack in a major UK hospital last year shut down MRI machines, insulin pumps and pacemaker devices connected to at-home systems that allow physicians to monitor the heart rate of patients.

> "We have been fortunate up to now [that] there has been no loss of life, that I know of, from a [hacked] medical device," Bessette said. "That will become a serious game changer if that happens." – Navigant Consulting's Jerry Bessette

USE THE 'HUMAN DEFENSE' TO PREVENT CYBERATTACKS

Bessette said that the key to preventing cyberattacks is the "human defense" – in particular, training all employees on the risk of exposure to cyberthreats from the minute they log into their computers and the internet. "Teach them to be vigilant through constant training on the different types of attacks that hackers use," he urged. *(Also see "Device-Makers Have Amped Up Defenses Against Hackers" - Medtech Insight, 9 Dec, 2016.)*

It is also important for a manufacturer to carefully vet third-party vendors that have access to its computer systems. Bessette said hacking breaches experienced by Target in 2013 and Home Depot in 2014 occurred because third-party vendors were not carefully screened, allowing hackers to use custom-built software to enter the firms' networks and hack into payment cards. The companies lost a significant amount of money from these breaches and the CEOs subsequently resigned.

He also recommends building more security into networks as the workforce becomes more remote, with "lots of folks logging in from outside of the hospital or health-care facility."

Lastly, he said that all companies should prepare for their systems to be targeted by hackers at any time. "If 25% of the effort goes to [preventing cyberattacks], we would have a much better world," Bessette said. "As I get on these phone calls with medical facilities that have been hacked, a lot of this does not happen at 12:30 pm on a Tuesday."

"We have been fortunate up to now [that] there has been no loss of life, that I know of, from a [hacked] medical device," Bessette said. "That will become a serious game changer if that happens and an individual passes away because their pacemaker stops working because of a malware attack."

Published online 08/22/17

In Austria, Industry Worries Over Loss Of EU Medtech NBs

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Do EU medtech notified bodies (NBs) impart a positive effect on the medtech infrastructure of the country or region where they are based? Is industrial activity more likely to develop in a region where all the tools – regulatory, trade links, research and government support – are available? At least one Austrian regional official thinks so, and is concerned for future medtech industry activity in Austria now that the only two nationally-based NBs have closed for medtech work.

Patrizia Zoller-Frischauf, the regional Austrian economy councilor for the state of Tyrol, affirmed in a statement that following the discontinuation of medtech auditing at TÜV Austria in Vienna and the Europaprüf- und Zertifizierstelle für Medizinprodukte (PMG) at TU Graz, Austria no longer has a notified body for medtech that can work under the EU MDR and/or IVDR.

Zoller-Frischauf fears that local companies will now have to undergo "complicated procedures" in other EU member states that are "further away and more costly." Such comments seem to run counter to EU ideals of a standardized, centralized model of pre-market medtech regulation, but it is a sign of deep-seated fears emerging, now that the MDR and IVDR are becoming reality. Similar concerns may also be rising to the surface in other EU member states.

Last week, a Swiss medtech CEO told *Medtech Insight* of his fears for the future of innovation, and indeed the medtech industry in Europe, now that NBs are beginning to feel pressure from the new EU regulations. *(Also see "Exec: EU May Lose Out On More Innovation As MDR Pressure On NBs Begins To Bite" - Medtech Insight, 21 Aug, 2017.)* In Switzerland, the number of NBs that perform conformity assessment work under EU medtech directives/regulations has dropped from seven to "one and a half" in a short space of time.

The EU NB association, TEAM-NB, recently reported that the number of NBs would fall to below 50, although just how far below is a question that can only be answered in a few years' time. It is what occurs in the interim that is scaring more and more people in the industry, and some in government circles too.

Zoller-Frischauf worries the local industry in Austria will not be able to compete, and "Standort Österreich" – Austria as a medtech business location – becoming less attractive. Highly-qualified jobs are at risk, and local research institutes like MedUni Innsbruck and UMIT (health and life sciences university) will be disadvantaged, she warns. She also fears a generally slower availability of innovations for use in the local patient population.

Pushing for the local NB situation to be addressed, she said, "Replacements must be set up as soon as possible to support innovative local companies and researchers." She is calling for solutions from federal health minister Pamela Rendi-Wagner. But local press reports, in the newspaper *Tiroler Tageszeitung*, appear to show the government in a defensive mood, with officials rolling out patient safety arguments and saying that costs should not rise under the new EU regulatory system.

THE EMA ANGLE

Perhaps it is a question of timing: Vienna is one of 19 EU cities (including Malta as a whole) that have applied to host the European Medicines Agency once it leaves London, as a function of the – to many, pointless, wrong-headed and energy-sapping – Brexit decision. *(Also see "19 Countries Have Submitted Bids To Host The EMA Post-Brexit" - Medtech Insight, 1 Aug, 2017.)* None of the candidates that submitted their applications by July 31 will be likely to display anything less than total solidarity with EU health-care policy for the time being.

Does that mean that medtech's problems are less important for EU decision makers? It shouldn't, but the NBs issue is doubtless not what the MDR and IVDR architects would have wanted or expected; many are already blaming those same decision-makers for what the Swiss medtech executive has called "a catastrophe in waiting."

Published online 08/24/17

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