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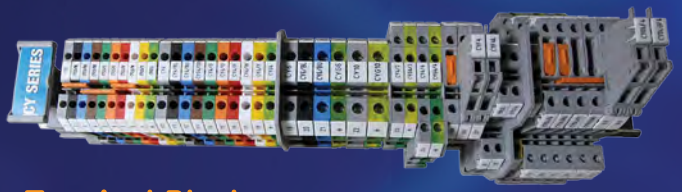

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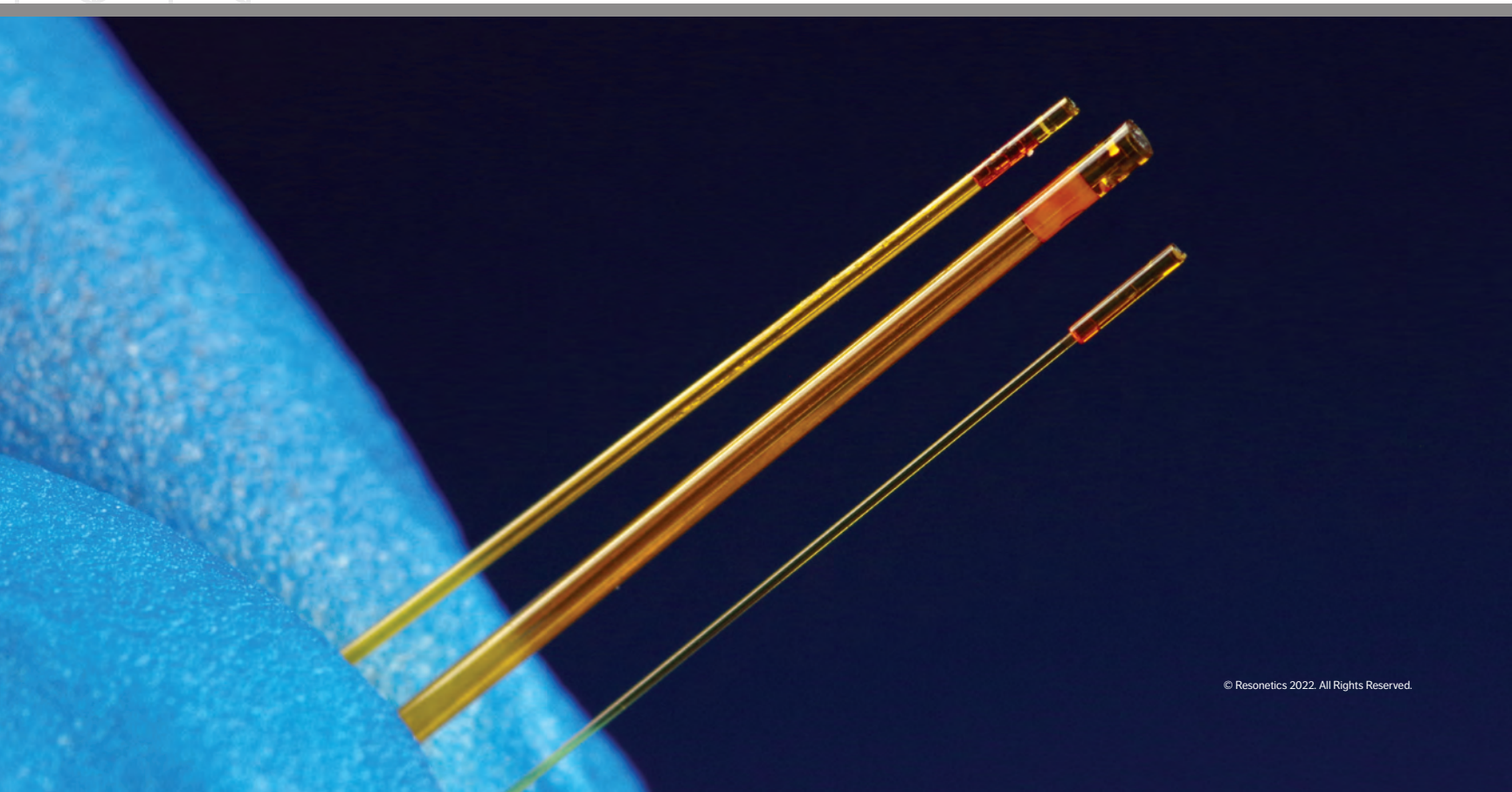

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Executive Editor
Chris Newmarker
cnewmarker@wtwhmedia.com
@newmarker

Managing Editor
Jim Hammerand
jhammerand@wtwhmedia.com

Senior Editor
Danielle Kirsh
dkirsh@wtwhmedia.com

Pharma Editor
Brian Buntz
bbuntz@wtwhmedia.com

Associate Editor
Sean Whooley
swhooley@wtwhmedia.com
@SeanWhooleyWTWH

Editorial Director - *DeviceTalks*
Tom Salemi
tsalemi@wtwhmedia.com

VP Lifesciences
Mary Ann Cooke
mcooke@wtwhmedia.com
781.710.4659

CREATIVE SERVICES

VP of Creative Services
Mark Rook
mrook@wtwhmedia.com
@wtwh_graphics

Art Director
Matthew Claney
mclaney@wtwhmedia.com
@wtwh_designer

Senior Graphic Designer
Allison Washko
awashko@wtwhmedia.com
@wtwh_allison

Graphic Designer
Mariel Evans
mevans@wtwhmedia.com
@wtwh_mariel

AUDIENCE DEVELOPMENT

Director, Audience Development
Bruce Sprague
bsprague@wtwhmedia.com

WEB DEV/DIGITAL OPERATIONS

Web Development Manager
B. David Miyares
dmiyares@wtwhmedia.com
@wtwh_webdave

Digital Media Manager
Patrick Curran
pcurran@wtwhmedia.com
@wtwhseopatrick

Front End Developer
Melissa Annand
mannand@wtwhmedia.com

Software Engineer
David Bozentka
dbozentka@wtwhmedia.com

Web Dev./Digital Production
Elise Ondak
eondak@wtwhmedia.com

PRODUCTION SERVICES

Customer Service Manager
Stephanie Hulett
shulett@wtwhmedia.com

Customer Service Rep
Tracy Powers
tpowers@wtwhmedia.com

Customer Service Rep
JoAnn Martin
jmartin@wtwhmedia.com

Customer Service Rep
Renee Massey-Linston
renee@wtwhmedia.com

Digital Production Manager
Reggie Hall
rhall@wtwhmedia.com

Digital Production Specialist
Nicole Johnson
njohnson@wtwhmedia.com

Digital Production / Marketing Designer
Samantha King
sking@wtwhmedia.com

Marketing Graphic Designer
Hannah Bragg
hbragg@wtwhmedia.com

DIGITAL MARKETING

VP, Digital Marketing
Virginia Goulding
vgoulding@wtwhmedia.com
@wtwh_virginia

Digital Marketing Manager
Taylor Meade
tmeade@wtwhmedia.com
@WTWH_Taylor

Digital Marketing Coordinator
Matthew Kulkin
mkulkin@wtwhmedia.com
@WTWH_Matt

Webinar Manager
Matt Boblett
mboblett@wtwhmedia.com

Webinar Coordinator
Halle Kirsh
hkirsh@wtwhmedia.com

Webinar Coordinator
Kim Dorsey
kdorsey@wtwhmedia.com

EVENTS

Events Manager
Jen Osborne
jkolasky@wtwhmedia.com
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Events Marketing Specialist
Olivia Zemanek
ozemanek@wtwhmedia.com

VIDEO SERVICES

Videographer Manager
Bradley Voyten
bvoyten@wtwhmedia.com
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Videographer
Garrett McCafferty
gmccafferty@wtwhmedia.com

FINANCE

Controller
Brian Korsberg
bkorsberg@wtwhmedia.com

Accounts Receivable
Jamila Milton
jmilton@wtwhmedia.com

WTWH Media, LLC
1111 Superior Avenue,
26th Floor
Cleveland, OH 44114
Ph: 888.543.2447
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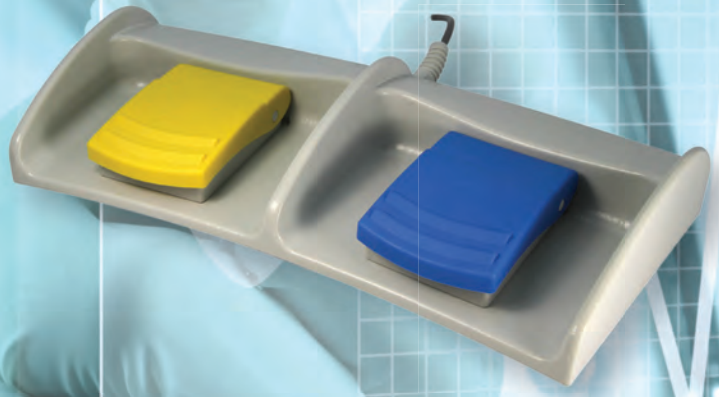

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Finding hope in small things

Two long years into the COVID-19 pandemic, with so much – and so many – lost to this virus, it helps to look for hope wherever we can.

Like flowers budding in spring, encouraging signs are slowly emerging. Vaccination levels are climbing every day in the U.S. and abroad, testing capacity continues to expand and new therapies are increasingly available.

There's no victory parade yet, and there might never be. But each small step in the right direction lets us incrementally reclaim pieces of our pre-pandemic life. How sweet it will be to greet friends and colleagues we haven't seen in a long time when we safely return to our in-person live events, starting with DeviceTalks Boston May 10–11.

This edition of ***Medical Design & Outsourcing*** is full of inspiring innovation where it's all about small: miniaturization.

In the following pages, experts at Mayo Clinic share their adventures in microscale 3D printing and its huge potential for the practice of medicine as their engineering unit tackles problems in support of researchers and clinicians across their organization. You'll also hear from Ilika about the millimeter-scale batteries that will power smarter, more compact rechargeable devices of the future.

Senior Editor Danielle Kirsh reports on some big catheter advances designed to navigate tiny spaces like Abbott's Amplatzer Piccolo Occluder device, designed specifically to be implanted in premature newborns without open-heart surgery.

Associate Editor Sean Whooley offers the latest on diabetes tech like a small, smart insulin pen cap that tells patients exactly how much of the drug they need.

Pharma Editor Brian Buntz takes us down to the molecular level, looking at potential applications for mRNA-based therapies following mRNA vaccines for COVID. Researchers are testing the use of mRNA to fight cancer, cardiac fibrosis, HIV, influenza and other diseases caused by bacteria and viruses.

Then meet Torrey Smith and the founding team of Endiatx, an early-stage startup that has developed a swallowable, wirelessly controlled robot that transmits live video as it swims inside the stomach. PillBot started with a prototype that was about the size of a large burrito or a 24 oz. aluminum can, and one day could become an even smaller remote surgical platform allowing for diagnosis and treatment without setting foot in a hospital.

And if you're still hungry for more about miniaturization, head to devicetalks.com for our March 22 DeviceTalks Tuesdays webcast with Isometric Micro Molding CEO Donna Bibber, who will discuss challenges and solutions for miniaturization in medical devices.

Please enjoy this edition of ***Medical Design & Outsourcing***, and take some time to appreciate the small things.

Jim Hammerand |
Managing editor |
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KATHLEEN DALEY is a partner at Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, and has significant experience in trial and appellate litigation. Her practice encompasses a wide range of technologies, such as mechanical devices, semiconductor devices, and pharmaceuticals, with a particular emphasis on medical devices.

SETH HARA is a Mayo Clinic Division of Engineering senior engineer and manager of the Microfabrication Laboratory. He has a background in bioMEMS and received his Ph.D. in biomedical engineering from the University of Southern California.

DENIS PASERO is product commercialization manager at Ilika, which has developed Stereax millimeter-scale solid-state batteries designed for powering active implanted medical devices.

DIDIER PERRET is the medical business development manager, Branson Welding and Assembly at Emerson. He has a degree in mechanical engineering from Technicum La Chaux-de-Fonds in Switzerland. Perret has worked for Emerson since 2000 and has extensive experience in automation, production, product design and plastics assembly technologies.

ANGELINE PREMRAJ is an attorney at Finnegan, Henderson, Farabow, Garrett & Dunner, LLP with a diverse patent practice in client counseling, prosecution, litigation, and post-grant proceedings before the Patent Trial and Appeal Board (PTAB) of the U.S. Patent and Trademark Office (USPTO). While her technical background is rooted in medical devices, she works with a broad field of technologies, including augmented and virtual reality (AR/VR), electrical and computer technology, financial and business systems, and manufacturing.

DAVID PTACEK is national sales director of Fischer Connectors, responsible for sales and product development in North America and Latin America. With more than 20 years of experience in the B2B interconnect industry, Ptacek works closely with top medical device manufacturers to co-create innovative products using the latest in connectivity technology.

RENC SARACAYDIN is pursuing a master's degree in materials science and engineering at University of California, Los Angeles, and is working on microscale additive manufacturing as a graduate microfabrication intern at Mayo Clinic.

TROY VIGER is an attorney at Finnegan, Henderson, Farabow, Garrett & Dunner, LLP with a broad practice covering patent litigation, prosecution, client counseling, trademarks and design patents. He has experience with a variety of technologies, including biomedical devices, numerical algorithms, virtual reality (VR), software, and calibration systems.

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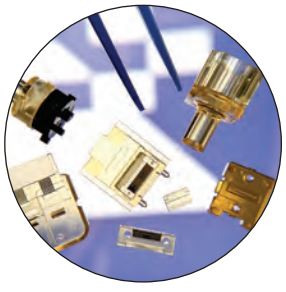

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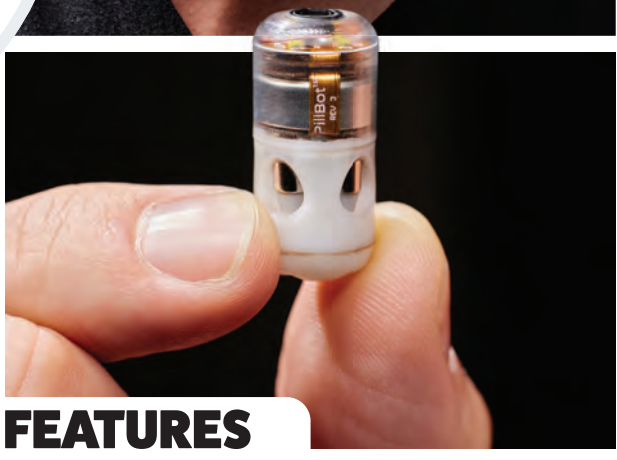
ON THE COVER

ENDIATX'S PILL-SIZED ROBOT SEES AND SWIMS INSIDE THE STOMACH

An unconventional CEO and his team take aim at endoscopies with faster, cheaper stomach imaging — and that's just the start. Welcome to the era of tiny robots inside the body.



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What is microscale 3D printing? Lessons learned from Mayo Clinic

Microscale 3D printing has the potential to revolutionize medical device development.

Seth Hara |
Mayo Clinic |

Renc Saracaydin |
Mayo Clinic |

The Mayo Clinic Division of Engineering is an embedded engineering team that provides engineering support and service for researchers and clinicians throughout the enterprise. To meet their needs, the engineering team has embraced the use of microscale 3D printing.

Microscale 3D printing in medical device development is still relatively new. As this technology continues to mature, the field will continue to find new and exciting opportunities to advance the practice of medicine.

As the name implies, microscale 3D printing is the use of additive manufacturing techniques to produce structures that have features as small as a few microns. To put everything into scale, a human hair is around 100 µm (microns) in diameter; that is one-tenth of a millimeter or four-thousandths of an inch. The ability to 3D print at such a small scale opens the door to a variety of applications in the biomedical sector.

This technology can additively manufacture 3D microfluidic chips to be used for diagnostic blood tests, cell sorting, drug discovery and organoid synthesis, to name a few applications. It can be used to fabricate drug delivery systems such as microneedle arrays to allow the self-administration of drugs or vaccines painlessly and effectively. Additionally, it enables manufacturing of porous architectures or scaffolds that can be used to guide the growth and proliferation of cells for regenerative medicine applications such as the treatment of spinal cord injuries. Beyond these cutting-edge applications, microscale 3D printing enables the fabrication of connectors, fixtures, and other auxiliary components that are essential for medical devices.

Microscale 3D printing takes shape

Over the last decade, a surge of 3D printing technologies have become commercially available. Some of the most common are material extrusion, vat photopolymerization, powder bed fusion, and material jetting. Even though these technologies are capable of manufacturing relatively large components with great repeatability and reliability, they often struggle to scale down the features below a couple hundreds of microns.

However, with advancements in optics, microelectromechanical systems (MEMS), and materials science, new technologies capable of microscale 3D printing have emerged. Proprietary names for some of these technologies are micro-stereolithography (µSLA), micro-digital light processing (µDLP), projection micro stereolithography (PuSL), and two-photon polymerization (2PP).

The working principle of these technologies is similar (except for 2PP, to be explained later). A viscous photopolymerizable resin is exposed to visible or ultraviolet (UV) light based on the geometry of the desired part. As light interacts with the resin, it cures the resin and turns it into a rigid polymer. Specifically, the energy provided by the UV light creates reactive species called free radicals that covalently bond to monomers and/or oligomers to initiate the photopolymerization reaction. *(continued on page 16)*

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"This is an exciting chapter for both additive manufacturing and medical device development. Microscale 3D printing is opening doors to new possibilities and providing tools for researchers and engineers to develop the next generation of medical devices."

As more molecules are bonded together, the reaction propagates until it is terminated. This reaction leads to long polymer chains that can be interconnected depending on the type of resin used. This process is repeated for each layer until the final part is realized. What allows these technologies to print in the microscale is their ability to highly localize the photopolymerization reaction through the use of customized resin chemistry and high optical resolution ranging from 1 to 5 µm.

On the other hand, 2PP operates in a different regime and utilizes resin chemistry that requires two femtosecond pulses to photopolymerize an extremely localized focal volume. This allows structures to be printed in free volume with submicron resolution, trading off the larger build volumes that can be accomplished with the former technologies.

Microscale 3D printing's challenges

As with any emerging technology, there are many challenges and obstacles that must be addressed to realize microscale 3D printing's full potential. New materials must be developed to leverage advancements in optical technology and processes must be tuned so that photopolymerization is contained to small volumes while adequately forming secure bonds.

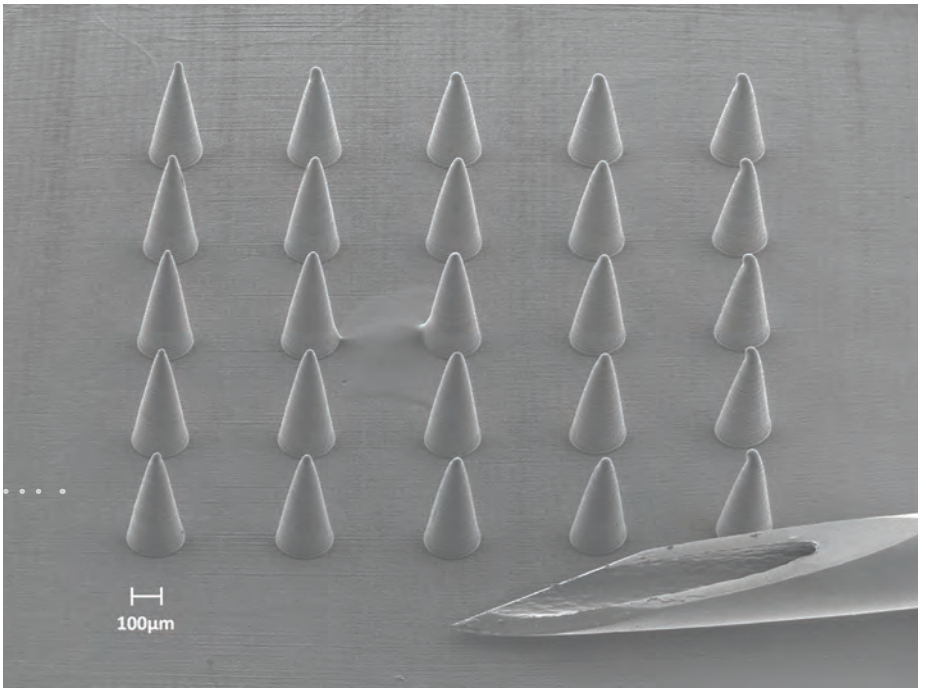
Once parts are printed, post-processing presents another round of challenges. As with any resin-based printing, uncured resin must be removed from cavities and lumens. This is often accomplished by immersing the part in a solvent bath and agitating the solution. Microscale prints, however, can be vulnerable due to their small features and so agitation must be done carefully — if at all — to prevent damage and breakage. This is made even more difficult by the intricate patterns and small volumes designed into microscale parts, which often require more agitation to properly remove all uncured resin. These competing requirements highlight the critical need for process tuning and design strategies for microscale prints.

Microscale 3D printing for medical device development adds an additional level of complexity to processing considerations. The materials that enable printing on the microscale often do not have a long history of biocompatibility and must be thoroughly tested for the intended application. Furthermore, the printing process itself must be evaluated and controlled to verify that the material properties of the final part are repeatable and safe. If the printed part is to be used in an application that requires sterilization, strategies must be put into place in the design stage to ensure that the selected sterilization process will not

negatively impact the material properties of the part and that all surfaces are properly sterilized.

This is an exciting chapter for both additive manufacturing and medical device development. Microscale 3D printing is opening doors to new possibilities and providing tools for researchers and engineers to develop the next generation of medical devices.

As the challenges facing this new technology are addressed, microscale 3D printing will likely be a common and enabling fabrication tool in this highly innovative field.



These 3D printed microneedles, viewed through a scanning electron microscope, are pictured next to a traditional 29-gauge hypodermic needle. A human hair is approximately as wide as the 100 micron scale marker in the image.
Image courtesy of Mayo Clinic

A hip implant powered by an Ilika battery
Image courtesy of Ilika

How tiny, solid-state batteries enable smaller implants that recharge faster

Denis Pasero | Ilika |

With a solid electrolyte, high energy density and thin packaging, solid-state batteries are getting smaller and enabling devices to be implanted in more parts of the body.

It has been more than six decades since Åke Senning implanted the first heart pacemaker in a patient. Even though today's pacemakers have improved treatment considerably, the same principles apply: Power is supplied from a battery to a pulse generator to maintain an adequate heart rate in the patient.

A similar principle can be applied to medical practices such as neuromodulation, which alters nerve activity through targeted electrical stimulus. Neuromodulation was originally developed to treat chronic pain through deep brain stimulation, but as the subject has become more widely understood, its use has spread from pain relief to other types of treatment, including for Parkinson's disease, pelvic disorders and angina.

Normally the patient has to attend a healthcare center for this type of treatment or use a battery pack to power the implant. If implants could be made smaller with an integrated power supply, then many more opportunities would be created.

For example, cardiac sensors and leadless pacemakers could be developed and implanted into the heart using a catheter. This type of treatment would offer many benefits: the surgery would be less intrusive, recovery time for the patient would be shorter with less risk of infection and the process itself would be much *(continued on page 20)*

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quicker and less costly. A better power source would also ensure that the implant could stay in place for a longer period of time, reducing the amount of surgery overall. Finally, wireless technology could be included to provide a higher level of information on the patient's condition through additional sensors in the implant. The same wireless technology could also be used to easily modify the programming of the device.

Solid-state batteries are key to shrinking implants

The main hold-up to designing smaller medical devices is the battery. The other main components that make up a neuromodulation device or a pacemaker have already been miniaturized, such as the microcontroller, power management integrated circuit and wireless controller.

Currently, the batteries that are mainly used for medical implants are bulky and non-rechargeable. If a patient has to have surgery to replace batteries, then it makes sense to put as much

Ilika's Stereax M300
solid-state battery
Image courtesy of Ilika

energy storage in place as possible to extend the time between surgeries. Rechargeable batteries would be ideal to extend the time between procedures even further, but historically patients have shown a low level of compliance when asked to charge them. There have also been other problems with rechargeable battery technologies, such as the liquid electrolyte used in lithium-ion technology having the potential to burst into flames.

However, there has recently been a breakthrough in battery technology that can provide medical developers with a smaller, rechargeable solution. Solid-state batteries use a solid electrolyte that is safe for patients, meaning that they don't need to have the bulkier metal packaging used by other batteries. They also have other advantages, such as a quick recharge time of around 10 minutes, which should offer a solution to the problem of patients neglecting to recharge batteries. The combination of a high energy density and a thin packaging means that solid-state batteries can be made much smaller while providing a similar amount of energy.

A practical example of a solid-state battery for use in medical implants is Ilika's Stereax M300, which will be available by the end of this year. The Stereax M300 uses energy dense chemistry and patterning to provide a capacity of 300µAh that can easily be recharged using energy harvesting technology. That capacity can be increased by stacking batteries together, or given a short-term output boost with the addition of a single capacitor when power demand is high. The Stereax M300 is under a millimeter high, and that form-factor is customizable. It is also safe and moisture resistant, making it ideal for use in medical applications.

The future of treatment

Although already proven, the technology behind solid-state batteries is still in its early stages. The Stereax M300 provides enough power for low-level electrical stimulation, such as that required for gastric stimulation, or vagus nerve stimulation to treat Parkinson's disease. Ilika has a product roadmap that will see the company launch a series of increasingly larger capacity batteries to provide medium-level stimulation for complaints such as sleep apnea, and finally larger-scale stimulation for chronic back pain and spinal cord stimulation.

Newer charging technologies will soon become available, allowing implant patients more freedom. In the short term, ultrasound technology will allow batteries to be recharged through the human body. In the longer term, directional wireless charging technology will be able to track an implant across a room and continuously top off its battery. Technologies like these will remove the responsibility of recharging from patients and allow the technology to be used in more life-critical applications.

There has recently been a breakthrough in battery technology that can provide medical developers with a smaller, rechargeable solution.

However, as the battery is a core function, it needs to be thought of during the design stage and not left to the end to see what batteries are available that might work. One size does not fit all. Engaging early and working with the battery manufacturer during the design stage enables the device the power to reach its full potential. Customized batteries will be designed around the device, rather than the device being designed around standard options.

With designers and battery suppliers working closely together, future medical implant innovations will deliver exciting results.

7 potential applications of mRNA-based therapies

The pandemic has accelerated research related to messenger RNA therapies across a range of disease areas.

Brian Buntz |
Pharma Editor |

Scientists have experimented with mRNA for decades, but the pandemic foisted the platform into the limelight. The Pfizer-BioNTech and Moderna COVID-19 vaccines have since emerged as two of the best-selling pharmaceutical products in recent memory.

Researchers are now exploring dozens of new possibilities for the mRNA platform. Here, we summarize several areas where mRNA could find use in the coming years.

1. Cardiovascular applications

Researchers at the University of Pennsylvania recently shared positive data related to the use of mRNA and CAR-T cell therapy to treat cardiac fibrosis in a mouse model.

And last year, AstraZeneca announced positive results from a Phase 2a study involving injected naked mRNA into the heart of patients undergoing coronary artery bypass surgery.

In 2013, researchers affiliated with Moderna published a report in *Nature Biotechnology* showing that an intramyocardial injection of mRNA encoding human vascular endothelial growth factor-A led to the expansion of endogenous heart progenitors in a mouse model of myocardial infarction.

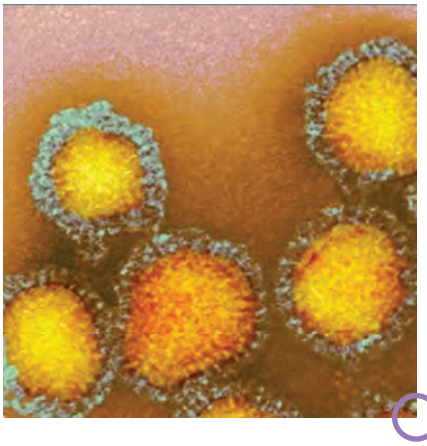
2. Flu

The basics of creating influenza vaccines have changed little for more than a half-century. Months before each flu season, drug companies first predict which strains are likely to predominate. Then, using chicken eggs or mammalian cells to grow flu virus strains, drug companies inactivate the viruses and process them into vaccines. The effectiveness of flu vaccines hovers somewhere between 40% and 60%, according to CDC.

The flexibility of the mRNA platform could improve the process. Pfizer claims it could make an RNA vaccine eight days after discovering a flu virus sequence. The company is partnering with BioNTech on the mRNA-based flu vaccine candidate BNT161, for which a Phase 1 study is underway.

Moderna is further along with its mRNA-1010 flu vaccine candidate. Interim results from a Phase1 study were positive but underwhelming, roughly in line with data from conventional flu vaccines. Moderna has two other developmental flu vaccines, known as mRNA-1020 and mRNA-1030.

Moderna and Novavax have combined COVID-19/flu vaccines in the works, while Sanofi intends to launch clinical trials for its SP0273 quadrivalent influenza mRNA-based vaccine candidate this year. *(continued on page 24)*



LEFT: MRNA injections are showing potential for heart health. *Photo courtesy of Raman Oza from Pixabay*
RIGHT: Artificially colored TEM image of H3N2 influenza. *Photo courtesy of Wikimedia Commons*

Go From Concept to Prototype

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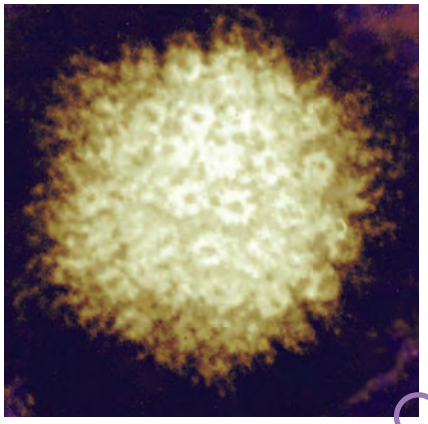
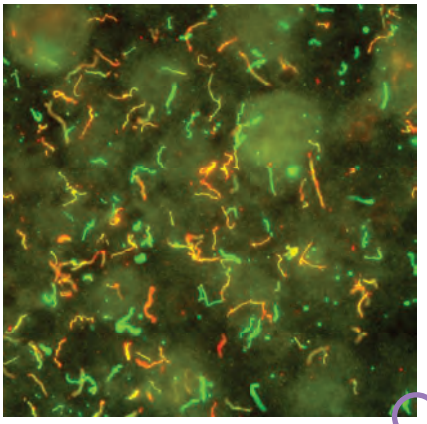




LEFT: Herpes zoster virus
Photo courtesy of Wikimedia Commons
RIGHT: Lyme disease spirochete, B. burgdorferi, a parasite, is shown using immunofluorescent antibody technique.
Photo courtesy of NIAID

3. Shingles
The global shingles vaccine market is big business and could be worth $6.35 billion by 2028, according to Grand View Research. The CDC says roughly 1 million people in the U.S. develop shingles — also known as herpes zoster — each year, with an incidence of four cases per 1,000 people annually.

GlaxoSmithKline's recombinant, adjuvanted Shingrix vaccine is the only FDA-approved vaccine for herpes zoster.

Pfizer and BioNTech have announced their plan to pursue an mRNA-based shingles vaccine, likely launching a Phase 1 trial this year.

4. Lyme disease
There are no Lyme disease vaccines on the U.S. market. GSK introduced a vaccine known as LYMErix in 1998, but the vaccine was pulled from the market in 2002 owing to low demand.

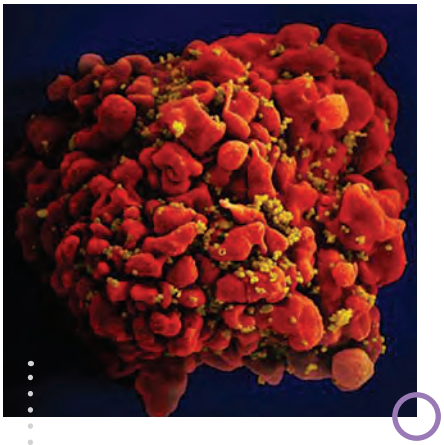
Researchers at Yale University are working on an experimental mRNA vaccine for Lyme disease. Last year, the experimental vaccine fared well in preclinical research involving guinea pigs. Targeting proteins in tick saliva, the experimental vaccine was featured in *Science Translational Medicine* in November 2021.

5. HIV
There are presently no licensed HIV vaccines, although researchers have attempted to develop them for almost four decades. Researchers continue to work on both prophylactic and therapeutic HIV vaccines. While the first type could potentially stop infection, the second would slow the progression of HIV in an infected individual.

Moderna has multiple prophylactic HIV vaccine candidates in the works in preclinical development: mRNA-1644 and mRNA-1574.

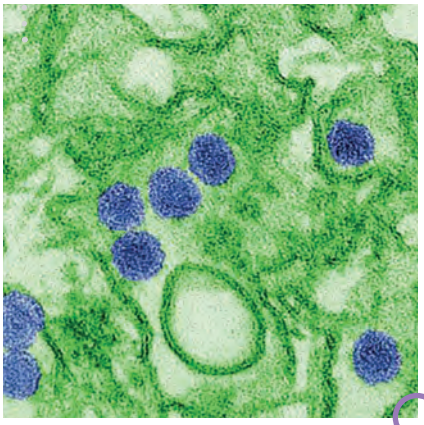
In August, Moderna announced a Phase 1 study to test two versions of its mRNA-1644 vaccine: as eOD-GT8 60mer mRNA Vaccine (mRNA-1644) and Core-g28v2 60mer mRNA Vaccine (mRNA-1644v2-Core).

Moderna's mRNA-1574 remains in preclinical development.



ABOVE: Scanning electron micrograph of an HIV-infected H9 T cell
Photo courtesy of NIAID

BELOW: A digitally-colorized transmission electron micrograph (TEM) of Zika virus
Photo courtesy of CDC



6. Cancer

Researchers have long suspected mRNA could be a promising platform for oncology. Indeed, efforts investigating the promise of the technology for cancer are ramping up.

Last year, Mayo Clinic researchers announced promising results using mRNA technology in conjunction with immunotherapy.

"We found that by introducing mRNA in immune cells, it is possible to produce useful proteins to improve their anti-tumor activity without attempting to change the genome itself," said Dr. Haidong Dong, a professor of immunology at the Mayo Clinic.

Moderna has several investigational oncology treatments in its pipeline, including mRNA-4157, a personalized cancer vaccine in Phase 2 trials. In the Phase 1 study, mRNA-4157 with Keytruda (pembrolizumab) was well tolerated and associated with tumor shrinkage in unresectable solid tumors and resected cutaneous melanoma.

Other experimental vaccines include the KRAS vaccine mRNA-5671 and mRNA-2752, which would potentially target solid tumors and lymphoma.

BioNTech has oncology product candidates in the works, including BNT111 for advanced melanoma, BNT112 for prostate cancer, BNT113 for HPV16+ head and neck cancer and BNT115 for ovarian cancer. BNT111 and BNT113 are in Phase 3 studies.

Phase 2 studies of BioNTech's BNT122 are additionally underway for first-line melanoma and colorectal cancer. BioNTech is working with Roche subsidiary Genentech on BNT122.

BioNTech is partnering with Sanofi on SAR441000, a saline-formulated mixture of four mRNAs targeting a solid tumor indication.

Finally, CureVac's experimental CV8102 mRNA vaccine showed promise in a Phase 1 clinical trial.

7. Zika

Zika remains rare in the U.S., but a pregnant mother can transmit the virus to her fetus, which can lead to microcephaly, a condition where a baby's head and brain are smaller than normal. While Zika rates in the Americas have plummeted in recent years, outbreaks of the virus are likely in the future.

In 2017, *Cell* published an article concluding that mRNA vaccines can protect against Zika virus infection. Moderna's mRNA-1893 Zika vaccine candidate is now in a Phase 2 trial.

Supreme Court's Arthrex decision creates more review for patent owners – and more questions

A Patent and Trademark Office director confirmation may solve some problems, but it's not yet clear how discretionary review will continue to evolve.

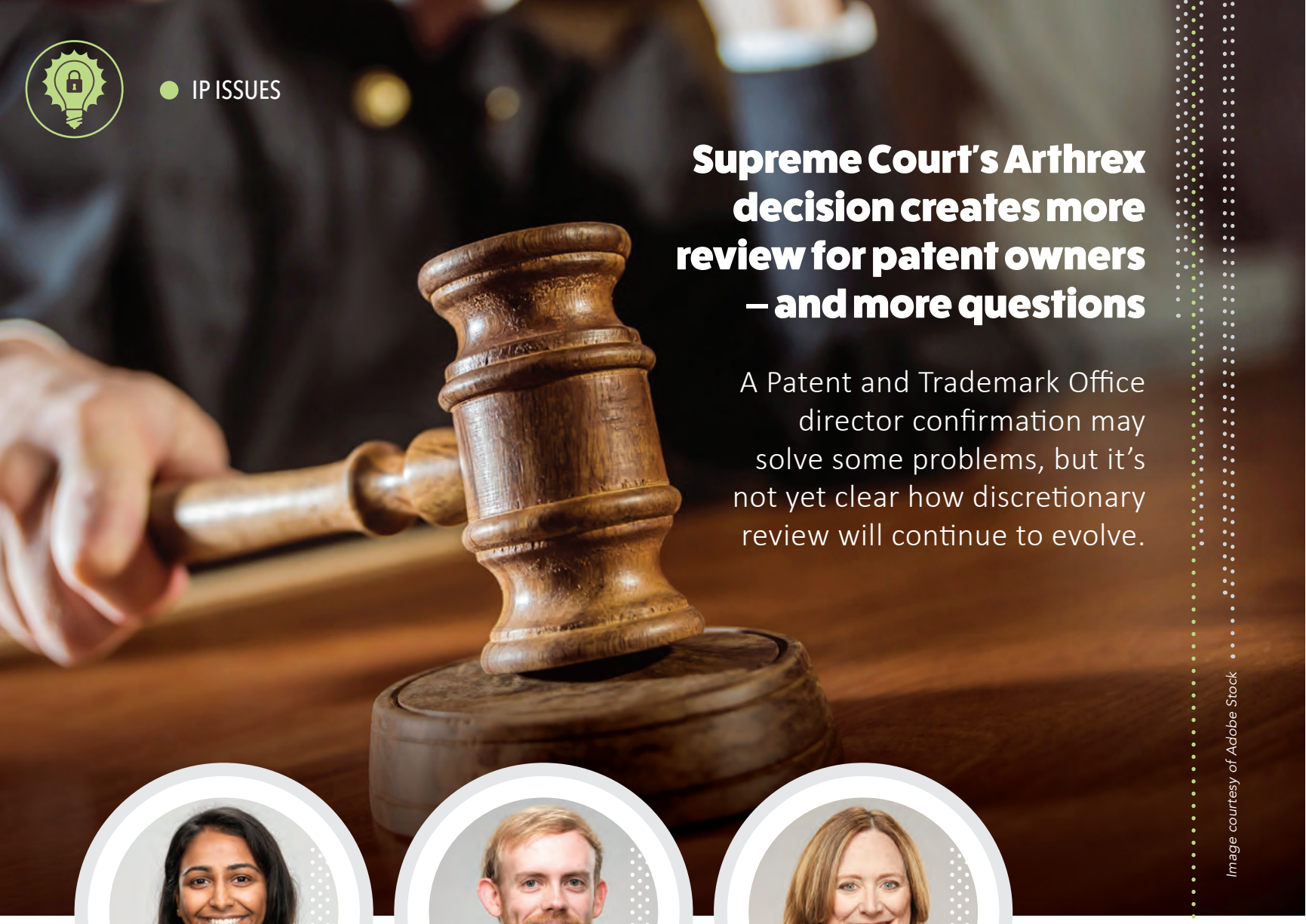


Image courtesy of Adobe Stock

Angeline Premraj | Finnegan |

Troy Viger | Finnegan |

Kathleen Daley | Finnegan |

The U.S. Patent and Trademark Office's inter partes review procedure is a popular avenue for challenging the validity of a patent outside of litigation. These procedures are overseen by a panel of three administrative patent judges (APJs) on the Patent Trial and Appeal Board (PTAB) at the Patent Office. In United States v. Athrex, the Supreme Court ruled that the "unreviewable authority" of APJs to conduct adversarial proceedings for challenging the validity of a patent violated the Constitution's Appointments Clause. The Supreme Court also ruled that the appropriate remedy was to give the director of the Patent Office the discretion to review those APJ decisions.

Arthex is the owner of U.S. Patent No. 9,179,907 (we'll refer to it as the '907 patent) which relates to a surgical device for reattaching soft tissue to bone without tying a knot. Arthex claimed that Smith + Nephew infringed the '907 patent, and the PTAB subsequently invalidated the patent in an inter partes review proceeding. On appeal, the U.S. Court of Appeals for the Federal Circuit ruled that the appointment of APJs violated the Appointments Clause. *(continued on page 28)*

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To remedy the violation, the Federal Circuit stripped away the APJ's tenure protections and sent the case back to the PTAB for a new hearing before a different panel of APJs. After the Federal Circuit denied requests for rehearing en banc and before the case went back to the Patent Office, the parties each sought Supreme Court review.

"Congress has assigned APJs [administrative patent judges] 'significant authority' in adjudicating the public rights of private parties, while also insulating their decisions from review and their offices from removal."

The Supreme Court took the case and agreed that there was a violation of the Appointments Clause, specifically taking issue with the fact that "Congress has assigned APJs 'significant authority' in adjudicating the public rights of private parties, while also insulating their decisions from review and their offices from removal."

The Supreme Court, however, fashioned a new remedy for the constitutional violation, holding "[d]ecisions by APJs must be subject to review" by the director of the Patent Office because Congress vested the director with the "powers and duties" of the Patent Office and tasked the director with supervising APJs. The Court held that the director may review final PTAB decisions (i.e., Final Written Decisions) and issue decisions on behalf of the PTAB.

Following the Supreme Court's decision, the Patent Office provided a procedure for director review (see https://www.uspto.gov/patents/patent-trial-and-appeal-board/procedures/arthrex-qas). The director may review a Final Written Decision on the director's own accord or, more likely, the director

may review a Final Written Decision in response to a party's request for director review. Once the request is submitted, the director may deny, or partially or entirely grant the request.

The director has since received more than 100 requests for review. In Proppant Express Invs. v. Oren Techs. (IPR2018-00733, Paper No. 94), the director vacated and remanded the PTAB's finding of unpatentability because it failed to give the necessary weight to objective evidence of nonobviousness. In Ascend Performance Materials Operations v. Samsung SDI (IPR2020-00349, Paper No. 57), the director similarly vacated and remanded another unpatentability finding because the PTAB failed to address the claims in view of their corresponding priority date. With the exception of these few outliers, petitions for director review under Arthrex have been largely fruitless, with the director denying most requests.

The current director review process is conducted under interim procedures. For now, a party receiving a Final Written Decision must choose to request either director review or rehearing by the original PTAB panel — it may not request both. Further changes to the review process may result in additional guidance for parties and the director.

Note that the Patent Office does not currently have a director that has been appointed by the president and confirmed by the Senate. As a result, there is some uncertainty regarding the legitimacy of reviews conducted by Drew Hirshfeld, who is currently performing the functions and duties of the director but has not been confirmed by the Senate. President Biden has nominated Katherine Vidal to the post, and her appointment has been approved by the Senate Judiciary Committee and forwarded to the full Senate for confirmation, which was pending at the time of this publication.

While the confirmation of a new director may solve some of the legitimacy problems associated with review, there may still be lingering questions as to the validity of review decisions issued by Hirshfeld. Moreover, it remains to be seen how discretionary director review will continue to evolve if and when Vidal is confirmed.

Selecting cables and connectors for your medical device

Connectivity for safety and performance is a complex consideration when designing modern medical equipment.

David Ptacek |
Fischer Connectors |

Connectivity products used in medical exoskeletons such as TWIICE must be robust, compact, lightweight and easy to use.
Photo by Alain Herzog for TWIICE

In patient care settings from surgical to imaging and diagnostics, therapeutics and patient self-care, the use of medical electronic equipment is ubiquitous and continues to grow. Advanced technology featured in new equipment and devices is bringing about ever more innovation to benefit patient experience and outcomes.

Such new designs typically need to integrate connectivity solutions: cables, connectors and electronics. Even though it may seem straightforward, connectivity today is a complex endeavor.

Connectors, cables and electronics are becoming more advanced in enabling electronic equipment to operate safely and reliably. If one connector fails, it could render the whole device inoperable, including the entire electronic ecosystem that was integrated with the device. This is one reason it is so important for connectivity solutions to be dependable in data transmission, robust in functionality and meet critical regulatory requirements.

Performance requirements vary and must also be considered when evaluating connectivity solutions.

Operational factors

Connectivity solutions must first ensure safety for medical personnel and patients, while offering a comfortable user experience and appropriate characteristics for the setting where they are used.

In an operating theater, numerous actors engage in a myriad of patient interventions. Surgeon operated headsets can be used to deliver optimal lighting during a procedure. To stop a cable from slipping into the surgeon's field of vision, a special 360-degree pluggable connector solution can ensure the cable remains in position while connected to the device, regardless of the surgeon's movements. *(continued on page 32)*

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Fischer Connectors products suited for medical devices include several types of connectors and associated cables (from left): Fischer Core Series Brass, Plastic, Disposable, Fischer MiniMax Series, and the Fischer Freedom Series. *Photo courtesy of Fischer Connectors*

In-home patient wearable applications provide additional examples that involve finding the right connectivity solution that is lightweight, durable, dependable, comfortable and easy to use.

Connectivity solutions have helped revolutionize modular and lightweight exoskeletons, where the motors at the joints require transmission between the joint and the controller. These connectors must be rugged for various environments and easy to clean. Weight can also play a role, one reason connectors are often manufactured from chrome-plated aluminum versus traditional heavier brass.

These examples demonstrate the versatility of connectivity solutions, especially where operational excellence is a key consideration.

Specification assessment

As you know, medical devices are highly regulated and must meet rigid certification requirements. For example, ISO 13485:2016, the internationally recognized quality systems standard for medical device manufacturers, also extends to their suppliers. This ensures that components are compliant, safe and reliable for integration into medical devices.

Environmental considerations can also impact connectivity design specifications. For instance, medical equipment connectors must be resistant to dust, dirt, debris and moisture incursion. In the case of liquid contact, connectors with IP68 sealing rates are protected from water ingress in both mated and unmated states. When sterilization needs arise, connectors and cables should be able to withstand high temperatures associated with autoclaving.

Durability and ease of use with connectivity solutions come into play when there are high numbers of mating cycles and frequent plug/unplug situations. A good measure is 10,000 mating cycles in cases such as diagnostic and imaging solutions. Connectivity action should be intuitive for all users — from trained to untrained — to alleviate issues with mating or damage to equipment.

When assessing weight and size considerations with wearables and in-home patient devices, connectivity solutions can be customized. With device miniaturization on a fast track, customized solutions that are compact, lightweight

and deliver the needed power and fast data transmission can support a successful and efficient deployment.

Selecting the right locking mechanisms

When mating connectors, several locking mechanism choices are available to meet requirements that aid the coupling and uncoupling of the mating parts. These mechanisms secure the connectors in an optimal operating position and assure the accurate electrical continuity and speed that is needed between the cable and the device.

Robust options entail push-pull, breakaway and screw. Blind mating brings benefits when connectivity lacks a clear line of sight. Color-coding identification is also popular.

Looking to the future

The future will bring new ways of treating disease and managing healthcare delivery. Medical devices will continue to evolve and dramatically enhance the practice of medicine. Many of these devices will require a vast range of connectivity solutions. The opportunities are endless with versatile and customizable connectors, cable assemblies and electronic solutions.

With IT-enabled and interoperable medical devices, electrical and optical connectivity solutions are playing a vital role in advancing product capabilities and will continue to be a contributor to innovative advancements in healthcare.

Plastics and medical devices: Changes for safety and cost

The move toward polypropylene and polyethylene in medical devices requires new manufacturing and assembly solutions such as ultrasonic and laser welding.

Didier Perret |
Emerson |

Plastics are ubiquitous in medical applications thanks to their light weight, durability and flexibility, among other attributes. However, concern has been increasing in recent years about the possible negative effects of some ingredients and components in certain plastics. This is leading medical-device companies to research and use other resins or combinations of plastics without the same risks. However, they do not have the same processing characteristic, and the changes often require companies to implement new production processes, especially around assembly and joining technologies.

For instance, polyvinyl chloride (PVC) is used in 40% of all plastic-based medical devices, according to Brussels-based PVCMed Alliance , and most tubing and IV bags available today, as well as many masks, breast-pump kits, catheters and more. Yet dioxin, a known human carcinogen, can form during the manufacture of PVC, and toxic chlorine may be released during processing and assembly. In addition, DEHP, a phthalate plasticizer commonly used to soften PVC, is a known endocrine-disrupting compound that is feared to leach into a patient's bloodstream and potentially cause fertility problems and other reproductive-related issues. For these reasons, healthcare and professional organizations including the American Medical Association, among other encourage hospitals and physicians to reduce and phase out the material.

Joining PVC components

The vast majority of PVC bags and other components are assembled using conductive (heat) welding, radio-frequency (RF) welding — also known as high-frequency or dielectric welding — as well as solvent welding and adhesives. As manufacturers have begun to explore alternative materials, particularly polyolefins such as polypropylene (PP) and polyethylene (PE), they are finding these traditional joining techniques are not effective, while other technologies offer cost reductions, sustainability improvements and safer toxicology for the product and along the entire production process.

PP and PE are nonpolar polymers, so they are impervious to the electromagnetic waves that generate heat during RF welding. Likewise, PP and PE have excellent chemical resistance and are not easily bonded using solvents, and their low surface energy also means adhesives are not very effective. *(continued on page 36)*

Ultrasonic systems (like Emerson's Branson GSX Ultrasonic Welding Platform, pictured) effectively bond alternative materials like PP and PE in medical applications, while radio-frequency welding commonly used with PVC cannot. *Photo courtesy of Emerson*

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By far the most effective technology for assembling polyolefins, as well as multilayer films incorporating these and other materials to form IV bags, is ultrasonic welding. Ultrasonic welding uses high-frequency vibrations to generate frictional heat between layers, softening the plastic so it merges into a high-quality seal when the films are held together under pressure. This is an extremely fast joining process that can be applied to almost any thermoplastic, including PVC. While the equipment costs are higher than other technologies, there are numerous benefits that ensure a relatively quick return on investment:

Medical tubing and other components that have historically been produced with PVC are being converted to safer and less costly PP and PE using ultrasonic assembly equipment. *Photo courtesy of Emerson*

- Energy savings: Unlike conductive welding, tooling does not need to be preheated and remains cool when not in use.
- No consumables: Adhesives and solvent are not required.
- Process efficiency: Welding times are short, allowing more cycles per minute.
- Nontoxic: No off-gassing occurs during welding, so there is no danger to operators and no need for expensive venting equipment.
- Green: All these factors contribute to a smaller carbon footprint than any competing joining method, including solvents or gluing.

Replacing polycarbonate

Polycarbonate (PC) is very strong, clear and dimensionally stable, making it ideal for many healthcare applications, including the tubular filter housings that are key components in kidney dialysis systems. However, it is known to contain bisphenol-A (BPA), another known endocrine-disrupting chemical that — like DEHP — can potentially cause a range of adverse health effects. It has largely been eliminated from use in baby bottles and water bottles used by athletes, and activist groups continue to call for an outright ban.

One of the reasons PC has not been totally banned is because low levels of BPA that find their way into the human body are easily eliminated by normal kidney function. However, according to recent studies, serum BPA levels accumulate as renal function decreases, and are highest in individuals with chronic kidney disease who are on hemodialysis. Hence, in dialyzer applications, manufacturers are looking for alternatives such as polypropylene.

Unfortunately, many of the limitations of PP as a replacement for PVC also apply to PC applications. Polycarbonate dialyzer housings have historically been assembled using mechanical fasteners and adhesives, neither of which works well considering the lower yield strength and lower surface energy of PP.

Consequently, manufacturers are here too turning to ultrasonic welding (with all the attendant benefits detailed above), as well as laser welding. In this latter process, components are pre-assembled before welding, and no vibration or movement is required to produce clean, particulate-free welds. Multiple laser beams apply energy along the full length of weld surface. One surface freely transmits the laser energy without itself being affected through to the second, laser-absorbing surface where laser energy is converted to heat conducted across the interface, creating the weld. Benefits of this process include:

- Weld quality: Localized heating/melting develops excellent cosmetic properties.
- Minimal flash and no particulate: No frictional motion and accurate power dissipation.
- Part design flexibility: Multidimensional joint configurations are possible.
- Gentle: There's no vibration, and minimal heating protects sensitive components.
- Fast and flexible: Ideal for high-volume applications.

Where to turn for help

As the industry turns from traditional materials like PVC and polycarbonate to cheaper, safer PP and PE, manufacturers are finding they can simplify their products, reduce costs and improve performance by shifting to ultrasonic or laser welding.

If you are seeking a new assembly solution to respond to market pressures that dictate a change in material, if you are seeking a new, more productive solution to your assembly needs, or even if you are already using ultrasonic and/or laser welding systems, Emerson and its Branson brand of products can offer support and assistance. Emerson takes a process-neutral approach to recommend the right technical solution for each application, and can make transitions as smooth as possible. Every Branson welding solution is backed by deep technical knowledge, decades of application experience, and a global supply chain with strong sourcing, manufacturing and customer-support capabilities. Ⓜ

As medical product manufacturers seek alternative materials for IV bags and related components, they are finding ultrasonic welding is effective and offers many additional benefits.
Photo courtesy of Emerson

The Velys robotic-assisted orthopedic surgical system
Photo courtesy of Johnson & Johnson

Danielle Kirsh |
Senior Editor |

How a robot revolution will reduce the physical burdens of orthopedic surgery

DePuy Synthes Worldwide President of Joint Reconstruction Andrew Ekdahl thinks robotic-assisted systems will be a big help for orthopedic surgeons who are busier than ever.

Innovations in surgical instruments and capabilities have substantially increased the volume of procedures being performed on any given day — and increased the physical burden on orthopedic surgeons.

Many years ago, the busiest surgeons would conduct three orthopedic procedures per week, said Andrew Ekdahl, worldwide president of joint reconstruction at DePuy Synthes. But now those busiest surgeons are performing more than nine procedures per day, multiple days each week.

"The physical burden of orthopedics has gone up dramatically. If we can do things to reduce that physical burden, that's innovation," Ekdahl told *DeviceTalks Weekly* podcast host Tom Salemi.

Surgical robots can help. Johnson & Johnson's DePuy Synthes won FDA clearance in January 2021 for the Velys robotic-assisted orthopedic surgical system for use with the Attune total knee implant. DePuy Synthes joined other medical device companies that have entered the orthopedic surgical robot market in recent years to compete against Stryker and its Mako robots. Other recent entrants include Smith+Nephew's Navio surgical system and Zimmer Biomet's Rosa knee system.

The Velys system adapts to a surgeon's workflow to give them the control needed to execute bony cuts efficiently and accurately. The table-mounted system is designed to easily integrate into any operating room. Its small footprint and

digital planning capabilities allow the robotic-assisted system to move between operating rooms and patient care rooms.

The system is particularly appealing to surgeons in ambulatory centers, as the site of care in the U.S. has rapidly changed due to the COVID-19 pandemic. Nurses, hospitals and care teams — along with surgeons — are experiencing burnout, and DePuy Synthes hopes that Velys will reduce some of the physical burdens.

"That is probably the biggest challenge that we'll face, the overall operation of hospitals in the near term," Ekdahl said. "I don't think it's going to last for a long period of time, because it will settle out. But that is going to have an impact."

The Velys robotic-assisted system is a part of DePuy Synthes' broader Velys Digital Surgery platform. Velys Digital Surgery is a platform of connected technologies that uses data insights to plan, execute and perform surgical procedures. It allows for real-time decision-making, increased precision and consistency and more personalized care, according to the company.

Velys Digital and the robotic-assisted arm eliminate the need for CT imaging prior to total knee implant procedures. It is based on a computer-assisted workflow that uses arrays and bony landmarks to enable surgical planning in the operating room at the time of the procedure.

The efficiency and accuracy of cuts and movements using Velys are attractive to surgeons, but it's the digital information capabilities in combination with the robotic-assisted system that make it unique, Ekdahl said.

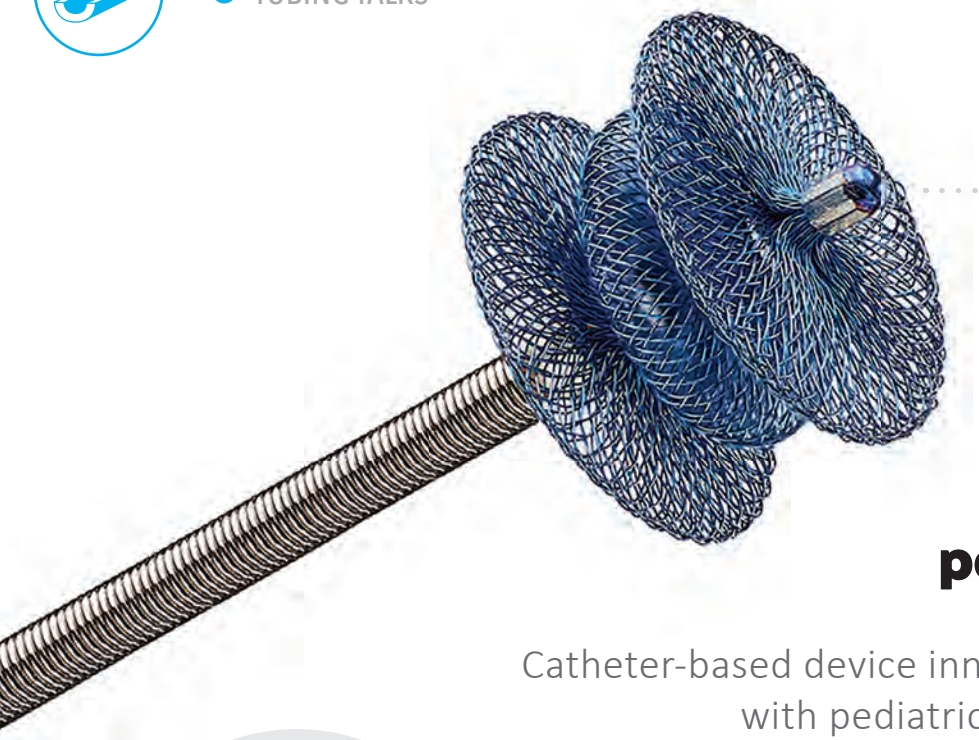
"Surgeons, initially when they use the robot, they're incredibly intrigued by the accuracy of the cuts," he said. "They're intrigued by the speed at which they can perform the procedure. What really intrigues them in the end is the ability to use the computer technology in combination with the robotic-assisted arm. It's their ability to use those two things and bring them together for a more accurate knee and a more well-balanced knee."

DePuy Synthes plans to bring more innovations to orthopedic robotic surgery now that elective procedures are returning to normal levels after being postponed due to the pandemic.

"Surgeons, initially when they use the robot, they're incredibly intrigued by the accuracy of the cuts."

The company wants to invest more in digital and enabling technologies to revolutionize robotic surgery using data that will in turn change implant designs in the future, Ekdahl said.

"If we can bring innovation to the table that reduces the physical burden of doing orthopedic surgery on the surgeon and the rest of the OR team to put the implant in, that's extreme innovation," he said.



Abbott's Amplatzer Piccolo occluder
Image courtesy of Abbott

Catheter innovations pour out of the pipeline

Catheter-based device innovations are picking up steam, with pediatrics seeing an influx of advances.

Danielle Kirsh |
Senior Editor |

Last year was a big year for catheter innovation as medtech companies large and small received regulatory approvals for devices ranging from TAVR to single-use endoscopes.

Catheter innovations weren't limited to just adults; catheter-deployed devices for premature babies and toddlers were also approved and released.

We looked back at last year's coverage at Medical Tubing + Extrusion to identify the catheter innovations that were of greatest interest to readers. The list includes devices from medtech giants like Stryker and Olympus, as well as smaller companies like EndoFresh and Preceptis Medical and a university-backed research team. Here are the 10 catheter-based innovations that dominated the news in 2021.

1. Abbott: Piccolo Occluder
The Amplatzer Piccolo occluder from Abbott is one of the first medical devices that health providers can implant in premature babies weighing as little as 2 lb to treat patent ductus arteriosus (PDA) in a minimally invasive way. While the Piccolo was approved by the FDA in early 2019, it gained a lot of attention in 2021 for its tiny structure with big impact. Piccolo is a self-expanding, wire mesh, catheter-deployed device that is inserted through a small incision in the leg and guided through vessels to the heart. It's designed to allow a physician to insert it through the aortic or pulmonary artery with the ability to retrieve and redeploy the device for optimal placement. Because of the device's small profile and its small market, the engineering behind the deploying catheter and device's material can significantly impact its efficiency.

2. Olympus: H-SteriScope single-use bronchoscopes
Olympus launched its product line of five H-SteriScope single-use bronchoscopes for tissue biopsy, foreign body retrieval and other advanced procedures to help clinicians target, diagnose and treat patients. They resulted from a collaboration between Olympus subsidiary Veran Medical Technologies and Hunan Vathin Medical Instrument. Each bronchoscope has a rotary function that allows insertion tube rotation up to 90° left and right and tip angulation range of 210° up and down.

3. EndoFresh: Disposable digestive endoscope
EndoFresh received FDA 510(k) clearance for its disposable digestive endoscopy system in May, featuring a camera system with an all-in-one design, disposable upper GI endoscope and disposable colonoscope, which can be used with the company's medical display and other peripheral devices for physicians *(continued on page 42)*

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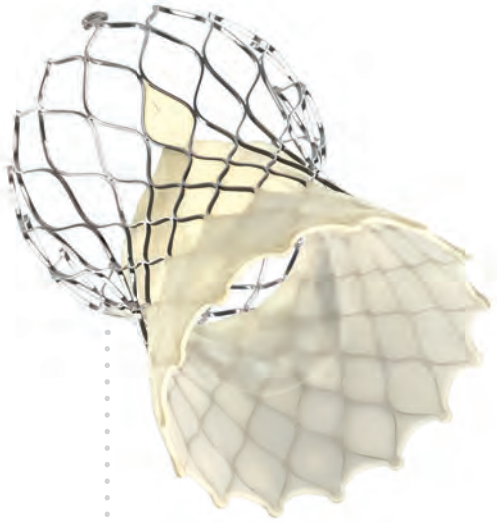
to visualize, diagnose and operate gastrointestinal endoscopy. EndoFresh is one of a handful of single-use endoscope designs that are saving lives. Boston Scientific and Ambu make fully disposable endoscopes, while Olympus, Pentax and GI Scientific make disposable protective components for endoscope end caps.

4. Stryker: InSpace balloon implant
Stryker received FDA de novo clearance for its InSpace balloon implant for arthroscopic treatment of massive irreparable rotator cuff tears in July. The implant is designed to restore the subacromial space without requiring sutures or fixation devices, and Stryker said it has demonstrated improved shoulder motion and function. The biodegradable balloon, which reduces friction between the acromion and the humeral head or rotator cuff, can be inserted arthroscopically or with a mini-open procedure.

5. University of California, San Diego: Steerable catheter for brain aneurysm treatment
Researchers at the University of California at San Diego developed a way to make steerable catheters that can precisely navigate the brain vasculature. Inspired by insect legs and flagella tail-like structures that allow microscopic organisms to swim, they designed the device to navigate the brain's arteries and blood vessels to treat aneurysms and other neurological conditions. The surgeon compresses a handheld controller to pass saline fluid into the catheter's tip to steer it. The steerable tip is visible on X-ray and has been successfully tested in pigs.

6. Medtronic: Evolut FX TAVR system
Medtronic won FDA approval in August for its Evolut FX TAVR (transcatheter aortic valve replacement) system for treating symptomatic severe aortic stenosis. The company said the self-expanding TAVR system's supra-annular valve design has demonstrated hemodynamic performance superior to surgical aortic valve replacement in large-scale, randomized clinical trials. Gold markers built into the frame provide direct visualization of depth and valve leaflet location during an implant, and a redesigned catheter tip provides a smoother



Medtronic's transcatheter aortic valve replacement (TAVR) Evolut FX
Image courtesy of Medtronic

insertion profile and a more flexible delivery system that has 360° freedom of motion with stable and predictable deployment. Like Medtronic's Evolut Pro+, the Evolut FX has four valve sizes for a large indicated patient treatment range and a low delivery profile.

7. Preceptis Medical: Hummingbird tympanostomy tube system
Preceptis Medical launched its second-generation Hummingbird tympanostomy tube system for office-based pediatric ear tube procedures in June. The device's ergonomic design provides more efficient ear tube delivery in children 6-24 months old. It allows ENTs to make an incision and deliver, position and place an ear tube using a single device in a single pass in a five-minute procedure that eliminates the need for general anesthesia and an operating room.

8. Boston Scientific: Exalt Model B single-use bronchoscope
Boston Scientific received CE mark approval for its Exalt Model B single-use bronchoscope in May. Designed for bedside procedures in the intensive care unit, operating room and bronchoscopy suite, Exalt Model B is available in slim, regular and large sizes for procedures such as secretion management, airway intubation, percutaneous tracheostomy, double-lumen endotracheal tube placement and biopsies. It's the latest single-use device from Boston Scientific, following the Exalt Model D single-use duodenoscope, LithoVue digital flexible ureteroscope, SpyGlass DS direct visualization system and SpyGlass discover digital catheter.

9. Cardiovascular Systems: OrbusNeich Jade balloon catheter
Cardiovascular Systems launched its OrbusNeich Jade percutaneous transluminal angioplasty over-the-wire balloon catheter in the U.S. in June. It's made for the peripheral vasculature, including obstructed native arteries and >>

Boston Scientific's Exalt Model B single-use broncoscope
Image courtesy of Boston Scientific

synthetic arteriovenous dialysis fistulae and post-dilation of balloon-expandable and self-expanding stents. The non-compliant balloon is designed for high-pressure tolerance and balloon dilation with even pressure distribution to treat complex lesions.

10. Micro Interventional Devices: MIA-T percutaneous tricuspid annuloplasty catheter

Micro Interventional Devices received FDA breakthrough device designation in May for the MIA-T percutaneous tricuspid annuloplasty system to treat moderate to severe tricuspid regurgitation. The 12F catheter-based system has an ergonomic handle with a safety and a button that deploys the implant. PolyCor anchors in the implant are loaded in the distal end of the delivery system and deployed into the tricuspid annulus in four-thousandths of a second. Micro Interventional submitted 12-month safety and performance study data for CE mark approval in December. The company said its study showed two and three grad reductions in tricuspid regurgitation that were achieved acutely and were maintained at 12-month follow-ups with no reported incidents of device or procedure-related mortality. Patients on the study reported an average improvement of 35% from baseline on the Minnesota Living with Heart Failure Questionnaire, the company said. Micro Interventional anticipated CE mark approval and IDE approval to initiate a pivotal trial in the U.S. by the end of 2021, but the company had not released an update as of this publication.

The distal end of the Micro Interventional Devices MIA-T delivery system is loaded with deployable PolyCor anchors. *Image courtesy of Micro Interventional Devices*

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Eyes on the prize

How Minnetronix helped Oculogica launch its new EyeBOX concussion diagnostic device

Jim Hammerand |
Managing Editor |

Less than three months after Oculogica won FDA clearance for its portable concussion diagnostic device, contract manufacturer Minnetronix is about to ship the first units to customers.

"We are aspiring to be a vital sign for brain health," Oculogica CEO Rosina Samadani told ***Medical Design & Outsourcing*** in an interview.

Diagnosing a concussion used to require asking a patient if they have a headache, fatigue, or nausea along with a host of subjective questions about how they feel in a 15- to 25-minute exchange.

The portable Oculogica EyeBOX EBX-4
Photo courtesy of Oculogica

The Oculogica EyeBOX test takes four minutes, measuring eye movement with a near-infrared camera that records gaze positions 500 times per second as a patient watches a video, then using an algorithm to calculate a BOX score. A score below 10 means no concussion, while 10 or higher indicates the patient is concussed.

The prescription device can be used on patients ages 5 to 67 within one week of sustaining a head injury. The test doesn't require any pre-concussion baseline or accurate answers from a patient who might have trouble communicating or an athlete motivated to get back on the field.

Samadani credited St. Paul, Minnesota-based Minnetronix for a fast launch following the latest regulatory clearance despite design changes and supply chain challenges.

New Richmond, Wisconsin-based Oculogica secured FDA 510(k) clearance for the new EyeBOX Model EBX-4 as a Class II device in December 2021.

The original EyeBOX won FDA De Novo classification in 2018. The FDA cleared the next two versions — adding Wi-Fi, swapping its wheeled chassis for a table-top enclosure and other modifications — through the 510(k) pathway in 2019 and 2020.

The new EyeBOX EBX-4 brings the most changes, starting with a weight drop from 34 pounds to just under 12 pounds and a reduction in volume from 6.3 ft^3 to 1.05 ft^3. The next-generation EyeBOX also adds a second camera and a rechargeable battery for power on the go.

The older, bulkier version is used by health care organizations such as the Minneapolis Clinic of Neurology and Chicago-based Midwest Orthopaedics at Rush. Both are interested in the portable version that can more easily move from room to room — or different sites, Samadani said.

Minnetronix helped Oculogica transfer the design from a research and development phase to manufacturing, optimizing the device from a supply chain perspective. More often than they'd like, even manufacturers like Minnetronix have products ready to go except for one or two components that are suddenly in short supply, said Matt Adams, VP and GM of Minnetronix's neuro, optics and fluids technology segments. The situation can delay manufacturing and end-of-line test development for months at a time.

"It's a relentless pursuit of not only the core vendors you're working with, but the brokers that are often coming in and buying out from underneath longtime customers," Adams said. "Your negotiating skills have got to be razor-sharp."

Minnetronix recently announced an optical medical device development partnership with INO Innovation Center, but Adams said that deal was too new to be part of the Oculogica project.

"We went to Minnetronix because they have specialized skills in ocular engineering," Samadani said. "We were really interested in that because we use eye-tracking ... we're looking at a lot of different things: how quickly they move, how well they move together, those types of things."

So what does the BOX in EyeBOX stand for? It's shorthand for "brain-injury-associated ocular motility dysfunction," a phrase coined by Samadani's neurosurgeon sister, Dr. Uzma Samadani, who runs the University of Minnesota's Neurotrauma Research Lab and founded Oculogica in 2013.

One of the most significant advances in concussion testing developed by Dr. Samadani is that the EyeBOX does not need pre-test calibration, which would require the device to have a look at a patient's eyes before they sustain a traumatic brain injury for comparison.

"It's called non-spatial calibration," Rosina Samadani said. "We're the only ones that have that."

Rosina Samadani wants Oculogica to expand to other areas of brain health, including elevated intracranial pressure, cognitive decline and traumatic encephalopathy syndrome (TES). TES is the clinical disorder associated with chronic traumatic encephalopathy (CTE), which can only be diagnosed with a post-mortem exam of brain tissue.

"We're very satisfied with where we are now, and we'd like to get it out to more people for concussion, [but] other areas of brain health ... are in our future," the Oculogica CEO said.

"We're very satisfied with where we are now, and we'd like to get it out to more people for concussion, [but] other areas of brain health ... are in our future."

Oculogica CEO
Rosina Samadani

Oculogica founder
Dr. Uzma Samadani

S

An unconventional CEO and his team take aim at endoscopies with faster, cheaper stomach imaging — and that's just the start. Welcome to the era of tiny robots inside the body.

Endiatx's pill-sized robot

SEES & SWIMS INSIDE

the stomach

JIM HAMMERAND
MANAGING EDITOR

PHOTOS FOR MEDICAL DESIGN & OUTSOURCING BY HARDY WILSON

As he prepared to swallow his robot for the first time, Torrey Smith's doctors warned that the battery was his greatest threat. If the capsule came apart and the battery burned the tissue lining his stomach, it would only be the beginning of a very bad experience.

"I was just hoping that we would get any kind of a positive signal that we were on the right track," Smith, co-founder and CEO of Endiatx, said of the June 2020 test. "At that time, our radio bandwidth was so limited. We were pushing 48 pixels square of grayscale, not even color, at just a few frames per second. The worst video quality you could imagine — but it was real."

The PillBot prototype's inaugural journey into Smith's gastrointestinal tract was a success, beaming live footage from his stomach without anesthesia, sedation, recovery time or air pumped into his gut to inflate it. >>

"My goal is to make it at least 10 times easier to just let a doctor have a look around inside you. A cheap, mass-market screening tool is what we think is the beginning for this adventure."

The latest prototype of the Endiatx PillBot is 28 mm long and 13 mm in diameter, with a camera at one end and four screw propellers at the other end.

"It almost looked kind of like the surface of the moon with that grayscale," he said. "But then we saw a dangling piece of tissue sloughing off from inside my stomach in real-time, and I literally shouted. Even with the extreme limitations of that revision, we were on to something."

Starting small

Less than two years after that first trial on the living room couch, Smith and his co-founders have swallowed more than 20 PillBots and tested the technology in a Mayo Clinic cadaver lab. They're now courting investors to raise $3 million in seed funding for the Redwood City, California-based startup as they look forward to clinical trials, FDA approval and commercialization.

It's not the first disposable pill camera. Medtronic's PillCam platform already captures images of a patient's esophagus, stomach, small bowel and colon as it goes with the flow through the GI tract. Nor is it the first single-use robotic pill. For example, Rani Therapeutics' RaniPill is designed to survive the stomach and deploy in the intestine. The pH change in the intestine unfurls the RaniPill to inject biologic drugs for conditions ranging from diabetes to Crohn's disease.

What's special about Endiatx's device is its propulsion system. Four tiny screw propellers push and steer PillBot through stomach juices and water, wirelessly directed by a Microsoft Xbox controller that will likely later be replaced with a smartphone app. Endiatx modified minuscule motors used to vibrate cell phones — 4 mm in diameter and 5.5 mm long — to power the screw propellers.

Another controllable, swallowable imaging device has been developed by AnX Robotica, which uses magnetic systems to precisely position its pill-sized camera during sedation-free examinations. That magnetic equipment means the patient must still visit the doctor, though it's less invasive than a traditional endoscopic gastroduodenoscopy (more commonly called an upper endoscopy) to search for cancers, infection, bleeding and other problems.

"Most of the time, we do an endoscopy to make sure there is nothing sinister going on. It's a diagnostic low-yield test, and for it to be invasive, that troubled me," said Dr. Vivek Kumbhari, the chair of gastroenterology and hepatology at Mayo Clinic–Florida. Kumbhari joined the Endiatx board in February 2021.

"Imaging in medicine is moving to non-invasive," he said, citing positron emission tomography (PET) scans, new types of computerized tomography (CT) scans and volume rendering. "Endoscopy is primed to follow."

Kumbhari, who performs about 1,300 endoscopies per year, recalled a lecture on the future of gastroenterology 15 years ago during his residency, specifically a hypothetical swallowable robot that could repair a stomach bleed.

Coincidentally, Endiatx's Pill Surgeon might be the next big iteration for this small device, currently assembled with about $35 worth of off-the-shelf components, Smith said.

"My goal is to make it at least 10 times easier to just let a doctor have a look around inside you. A cheap, mass-market screening tool is what we think is the beginning for this adventure," he said. "Then we start putting on the robot arms and the little snippers and tools and needles."

Simple tissue biopsies would likely come first, though there's also demand from doctors for ways to mark tissue so they can locate it later for reexamination. Other ideas range from bleed cauterizing to microbiome sampling in the GI tract and voyages through bile ducts to search for early signs of pancreatic cancer.

Endiatx plans to seek FDA clearance for PillBot as a Class II medical device on a 510(k) predicate-based pathway based on prior approvals of AnX Robotica's magnetic NaviCam and Medtronic's at-home PillCam. The goal is to pursue indications that can be achieved without too many improvements to the device, such as

Endiatx CEO and co-founder Torrey Smith poses in his warehouse shop in Oakland, California.

diagnosis of stomach lesions, ulcers and bleeds in a bid to enter the market as soon as 2023.

"Our regulatory consultants are saying this looks like one of the easiest 510(k)s they've ever explored," Smith said. "It just squirts water out the back. It's not really that scary."

Smith said he's been laughed at dozens of times during pitches, but he doesn't take it personally.

"The idea is to start somewhere tangible, drive it down step by step, learn as you go," Smith said. "It's okay if you get your butt kicked in different ways at every step. By the time we started swallowing this on our couch, we started getting a new kind of interest."

"I personally like people who aren't your usual polished execs. These are the out-of-the-box kinds of things we like to see."

The large prototype pictured below is called FishTankBot after its test habitat, and smaller versions eventually led to the swallowable PillBot. The Endiatx team tested an earlier, larger precursor called PoolBot (not pictured) in a swimming pool — and secured an investment from the pool's owner, CEO Torrey Smith said.

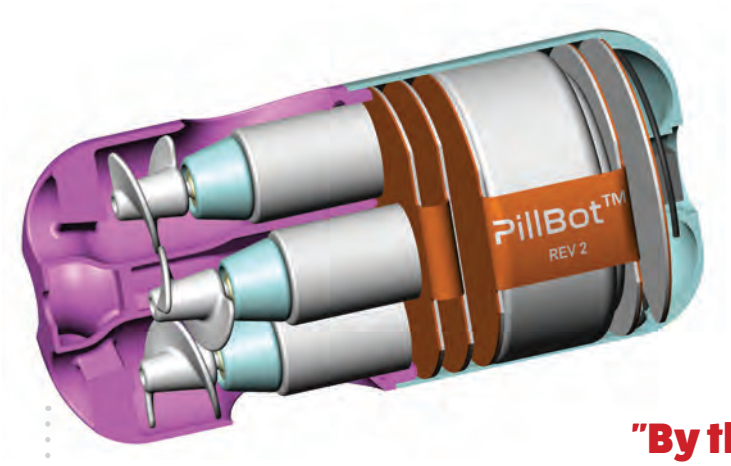
'Hardcore telemedicine'

Investors might be understandably reluctant to back a CEO who says he's been fired from nearly every job he's held and let strangers he met on the playa at Burning Man race PillBots inside him. Endiatx says in its pitch deck that it raised about $1 million from family, friends, angel investors and early-stage venture capital investors, and secured commitments for $1.8 million in seed funding.

"It doesn't look like they've raised much capital, and the non-buttoned-up CEO could be part of the reason," said Paul Grand, CEO and founder of the MedTech Innovator startup accelerator. "I personally like people who aren't your usual polished execs. These are the out-of-the-box kinds of things we like to see."

Smith's rallying cry is "hardcore telemedicine," the idea that diagnosis and treatment should be simpler, faster, less expensive and available beyond the walls of a medical facility. PillBot is the minimum viable product, Pill Surgeon is the next step, and from there it gets more advanced, Smith said, imagining a swarm of surgical drones each the size of a grain of rice and smaller versions after that.

"We have to drive this all the way down to the molecular level. Can I do that? … I'm probably not the one who's going to be doing molecular machines," said Smith, a mechanical engineer who previously designed atherectomy



Four tiny screw propellers push and steer the Endiatx PillBot. *Image courtesy of Endiatx*

"By the time we started swallowing this on our couch, we started getting a new kind of interest."

catheters. "What we're really building is the concept of normalcy of what we call hardcore telemedicine. We want a reliable platform where you can swallow a pill in your living room, but a doctor anywhere on the planet — or off-planet — controls it remotely."

He hopes his self-described "maverick spirit" will be balanced and complemented by Kumbhari. Others adding clout to the Endiatx team include co-founder, Chair and Chief Technology Officer Alex Luebke (previously at Google X/Loon in advanced tech development), co-founder and Chief Technology Officer Emeritus Dan Moyer, and co-founder and Principal R&D Engineer James "Heavy Metal" Erd, a metalworking wizard who was building spherical fuel tanks for the Google Lunar X Prize challenge when he first met Smith.

To build trust with doctors, future patients and potential investors, Endiatx posts videos from its R&D efforts online in an unusually transparent approach. But winning over investors might just come down to commercial opportunity. >>

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The global endoscopy market is expected to boom this decade, driven primarily by GI diagnosis and surgery. Estimates vary because the endoscopy business is massive and rapidly expanding, but most projections put market growth well into double digits, climbing to $50 billion, $60 billion or even $70 billion by 2030.

Smith emphasizes that Endiatx intends to compete with in-person endoscopies, not passive pill cams, to win market share, improve care and allow doctors to treat more patients.

"If PillBot, the cheap mass-market screening tool, can be effective and safe and make upper endoscopies a lot easier, Endiatx is a billion-dollar company at the minimum," Smith said. "We want to IPO this thing. … We're in this for the long haul."

Until then, the team continues a wild ride that has already taken them on a zero-gravity flight aboard a Cessna 310 as they worked on PillBot's swimming skills. Buoyancy is key, and in the way you might imagine the Endiatx team to circumvent flotation issues, they brought the device in a water tank aboard the twin-engine aircraft and had the pilot execute a maneuver to simulate weightlessness.

Dr. Kumbhari wasn't on that flight, and he's not among those who have swallowed a PillBot.

"Apart from the added excitement when you're trying to raise money or when you're presenting, there's not a whole ton of value doing it now," he said. "Once optics are improved — which is a simple thing to do, and Alex will work on that when the time's right — and the form factor and buoyancy are optimized, then that's the time to start swallowing. Then I think it'll be a whole lot of fun."

Endiatx board member and chair of gastroenterology and hepatology at Mayo Clinic–Florida

Dr. Vivek Kumbhari

Photo courtesy of Dr. Kumbhari

Image courtesy of Adobe Stock

Diabetes tech is off to a hot start in 2022

Diabetes technology developers have high hopes for the year ahead, some of which have already come to fruition.

SEAN WHOOLEY
ASSOCIATE EDITOR

Dexcom's next-generation G7 has demonstrated strong accuracy and is 60% smaller than the current G6 device. *Photo courtesy of Dexcom*

Change is continuous in continuous glucose monitoring (GCM), with expanded wear-times, improved accuracy and more. Meanwhile, never-ending innovation in insulin delivery is delivering wearable patches and closed-loop delivery systems, making insulin management easier for people with diabetes.

Expectations were already high for new technology coming out of the diabetes space, and significant improvements last year only lifted those hopes higher. Let's check in with a few companies promising big steps forward, including some that have already made significant progress.

Dexcom and its next-gen G7 CGM

San Diego-based Dexcom took several steps forward last year.

The company touted positive data regarding the accuracy of its next-generation G7 CGM and announced a significant regulatory nod and partnership for real-time application programming interfaces (APIs).

Dexcom also introduced the Dexcom One platform in a handful of European countries. Dexcom One uses the G6 hardware platform with a different software experience, marking the company's first foray into a differentiated product portfolio.

"2022 holds about more activity than we've ever seen in a given year," Dexcom CEO Kevin Sayer said in an interview. "It's going to be a year of many of the same activities, but some very big advances on the product front. And then once we get the hardware platforms out there, we're hopeful we can start coming up with several software solutions that are going to be different than what we've had in the past. It's going to be a fun year."

G7 won CE mark approval this month, and there is a sense among some analysts that it could receive FDA 510(k) clearance by June. >>

Bigfoot Unity's first-of-its-kind smart pen cap incorporates integrated CGM data and health care provider instructions to recommend insulin doses. *Photo courtesy of Bigfoot Biomedical*

"My people tell me in my own evaluations, 'You're not very good at celebrating, you always want to push,' but we recognize what a great year this company has had — really the past two years during these trying times," Sayer said. "We've grown almost a billion dollars in revenue in two years when the world has been nearly at a standstill. That's awfully, awfully amazing. It's been a great time period for us."

Bigfoot and a 'holistic' offering

Bigfoot Biomedical made its Bigfoot Unity diabetes management program available in select U.S. markets last year, launching what it sees as an all-in-one offering that could disrupt the diabetes space.

Bigfoot co-founder and CEO Jeffrey Brewer calls Bigfoot Unity a "transformational attempt" to simplify CGMs and the data they produce. It's comprised of a smart insulin pen cap that

The Bigfoot Unity was designed for managing insulin-requiring diabetes with multiple daily injection therapy. *Photo courtesy of Bigfoot Biomedical*

takes data from a CGM and informs a patient of exactly how much insulin they need at a given point in time.

The Milpitas, California–based company partnered with Abbott to integrate Abbott's FreeStyle Libre 2 CGM sensor into Bigfoot's system, letting Bigfoot's pen caps "talk" to the FreeStyle Libre.

Everything in Bigfoot Unity comes in one box, with the "holistic" platform trained by Bigfoot and supported by Bigfoot as opposed to different components provided by different companies. The platform also supports patients who are switched from one brand of insulin to another, sending them a new pen cap that fits with the insulin pen from the new manufacturer.

"People don't want data. They want to know what to do and how to stay safe and that's what Bigfoot Unity does. … We think it really points the way forward in terms of the consumerism of healthcare," Brewer said. "It's a great example of how you can make something simpler, easier and more accessible to a large population of people."

Senseonics and the six-month sensor

Senseonics Chief Medical Officer Dr. Francine Kaufman said in January that FDA approval for its next-generation Eversense E3 CGM was "imminent," echoing what the company had been saying for some time. In February, that approval finally came. >>

Germantown, Maryland–based Senseonics designed the Eversense E3 with proprietary sacrificial boronic acid (SBA) technology to extend longevity to 180 days, or six months. Senseonics previously offered the system with a 90-day wear time.

Senseonics already has eyes on the next steps. They include extending durability to one year, a mark that could be reached with the help of chemistry modifications and fundamental changes in the sensing surface itself.

The company also plans to push calibration frequency to once per week and add a battery center that won't increase the diameter but will marginally increase the length, allowing the transmitter to be taken off so the device can be used as an intermittent scanning device with other devices such as a smartphone.

"I still think that we'll need CGM to be sure things are working well and to understand part of our physiology better," Kaufman said. "What better device for that in the future than an implantable one that could last a year that you could query when you want to? And when you don't, you don't have to get that information. I'm just excited that we'll have something that will be meaningful through this next evolution of how we manage diabetes." M

OTHER BIG STEPS FORWARD

While Dexcom, Bigfoot and Senseonics have all made great strides in the diabetes space, they aren't moving forward alone.

In January, Insulet announced that it received FDA clearance for Omnipod 5, its next-generation automated insulin delivery system. The latest version of the Acton, Massachusetts-based company's wearable insulin delivery pump system covers individuals ages six years and older with Type 1 diabetes. The platform provides easier glucose management, with no multiple daily injections, no tubes and zero fingersticks.

In February, San Diego-based Tandem Diabetes Care announced FDA clearance of bolus insulin dosing on the t:slim X2 insulin pump using the t:connect mobile app. The t:connect mobile app is now the first FDA-cleared smartphone app for insulin delivery on both the iOS and Android operating systems. M

The Senseonics Eversense E3 wearable CGM system doubles the previous 90-day wear time to 180 days. *Photo courtesy of Senseonics*

"People don't want data. They want to know what to do and how to stay safe."

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SHOW PREVIEW

Tom Salemi | DeviceTalks Editorial Director |

Back to Boston

DeviceTalks Boston returns with a unique approach for medtech connections and development.

A few months back, I wrote what was best described by a colleague as a "salty" column in which I demanded conference organizers like myself step up our game if we expect to bring back attendees.

"For too long, conference organizers have relied upon a potent cocktail of FOMO and habit," I wrote in one particularly briny portion. "Sure, organizers try to amp up content, introduce cool partnering apps and a few gimmicks. (One recent healthcare meeting had puppies, actual puppies ... gimmicky, but intriguing.)"

Here I am, four months later, and I still agree with me!

We've been working harder — and smarter — to assemble the agenda of DeviceTalks Boston, coming up May 10-11 at the Boston Convention and Exhibition Center. And while I can't deliver puppies, I can promise you this unique approach will maximize your opportunity to build your knowledge and your networks.

Before I explain the new approach, let me reintroduce you to our DeviceTalks in-person meetings. We meet three times a year: first in Boston, then in Minnesota and finally in

Images courtesy of Adobe Stock

Santa Clara, California. Each of our meetings will create opportunities for engineers, innovators, manufacturing professionals and everyone else who touches a medical device in the product development process.

While we cover a wide range of medical device development issues, our events are targeted. Attendees won't need to navigate a maze of booths or hallways to make the right connections on-site. Our agenda will be equally disciplined. Our keynotes and conversations will fall into tight tracks: Product Development, Manufacturing and Supply Chain, Regulatory and Reimbursement, Digital Tools and Technology, and Innovation and Investment.

Now, back to the agenda. In crafting our upcoming DeviceTalks conference agendas, we're building discussions that will help medical device professionals at leading medical device companies hone their own skills. To bring real-workplace discussion to our stage, we partnered with leading medical device companies to develop Professional Development programs in each of our agenda tracks.

These are just some of the conversations we'll have at DeviceTalks Boston:

PRODUCT DEVELOPMENT

Abbott – Where is Heartmate headed in the future?

A team of engineers led by ***Kevin Bourque***, division VP of research and development, will examine the extraordinary success of the HeartMate 3 left ventricular assist device (LVAD) and explore what's next for this life-prolonging device.

KEVIN BOURQUE

Boston Scientific – How Boston Scientific uses clinical feedback to advance innovation

In this session, ***Meghan Scanlon,*** SVP and president, urology and pelvic health, will sit down with Jenny Lee, VP, corporate digital and patient and referrer marketing, to break down how company engineers leverage voice of the customers to advance meaningful innovation.

MEGHAN SCANLON

Medtronic – The road to the robot

Medtronic moves closer to bringing the Hugo robotic-assisted-surgery system to the U.S. In this conversation, ***Tracy Accardi***, VP of R&D, surgical robotics, and ***Mike Stow,*** VP of marketing, surgical robotics, will examine Hugo's past and lay out its future path.

MANUFACTURING AND SUPPLY CHAIN

DePuy Synthes – Journey from a medical device to medtech organization

Senior leaders from DePuy Synthes will discuss how the company is changing its product development process, setting up the supply chain for a medtech organization, learning about regulatory and access requirements for a digital solution, evolving our commercialization plans and using technology to amplify the effectiveness and reach of our education solutions. ***Rajit Kamal***, worldwide president of DePuy Synthes sports medicine and shoulder reconstruction, will lead the discussion.

RAJIT KAMAL

DIGITAL TOOLS AND TECHNOLOGY

Stryker – How Stryker is building out a digital surgery strategy

Stryker jolted the medical device industry in 2013 with its acquisition of Mako, giving needed validation to the nascent surgical robotics space. In this panel, the company's senior leaders — led by ***Spencer Stiles***, group president of orthopedics and spine — will reveal its data-centric digital surgery strategy to ensure that robotic surgery fulfills its promise.

SPENCER STILES

INNOVATION AND INVESTMENT

MedTech Innovator

The largest life sciences incubator in the world brings its road show to DeviceTalks Boston. Over two dozen mid- to late-stage privately held medical device companies will share their stories in hopes of finding investors and partners who will enable them to get their products to market. Conference favorites will compete in a pitch contest on May 11 with the winners chosen by attendees. MedTech Innovator founder and CEO ***Paul Grand*** will lead the presentations. If you're a company that has raised a Series B or Series C round, apply to present at medtechinnovator.org.

PAUL GRAND

I'm grateful to these companies for agreeing to use our community platform to connect with others in the medical device industry. If you're eager to understand how these medtech leaders get the job done, I would love to see you in Boston!

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on twitter **@MedTechDaily**

SALES

Ryan Ashdown
216.316.6691
rashdown@wtwhmedia.com

Mary Ann Cooke
781.710.4659
mcooke@wtwhmedia.com

Courtney Nagle
cseel@wtwhmedia.com
440.523.1685
@wtwh_CSeel

Jami Brownlee
224.760.1055
jbrownlee@wtwhmedia.com

Jim Dempsey
216.387.1916
jdempsey@wtwhmedia.com

Jim Powers
jpowers@wtwhmedia.com
312.925.7793
@jpowers_media

Ashley N. Burk
737.615.8452
aburk@wtwhmedia.com

Mike Francesconi
mfrancesconi@wtwhmedia.com
630.488.9029

Brian Toole
267.290.2386
btoole@wtwhmedia.com

LEADERSHIP TEAM

Managing Director
Scott McCafferty
smccafferty@wtwhmedia.com
310.279.3844
@SMMcCafferty

VP of Sales
Mike Emich
memich@wtwhmedia.com
508.446.1823
@wtwh_memich

EVP
Marshall Matheson
mmatheson@wtwhmedia.com
805.895.3609
@mmatheson

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