

Insight: implantable medical devices

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Implantable electronic medical devices have achieved remarkable medical advances in the treatment of the most challenging conditions, starting with the introduction of the first implantable pacemaker in 1958. Increasing demand for innovation in existing and novel implantable devices is fuelled by the growing aging population and the increased prevalence of chronic diseases. This perspective article provides an overview of the implantable medical device ecosystem, highlights recent developments, and discusses challenges and opportunities for translation of new innovative implants enabled by microtechnologies and microfabrication.

Introduction

Implantable medical devices have existed since ancient times; however, the current industry is largely enabled by a series of exciting advancements starting with the first implantable pacemaker in 1958. Close collaboration of industry, academia, and the medical community not only led to many new implants for treating a variety of diseases but also to the establishment of a new implantable device industry. According to the Freedonia Group, the demand in the US for implantable medical devices is projected to rise 7.7% annually to \$52B in 2015.⁴ The largest market segment today is

that of orthopedic implants which provide joint and bone replacements. Other major categories include cardiovascular implants (including pacing devices, stents, and structural implants), neurostimulators, and drug implants. This wide range of devices addresses treatment or diagnostic needs for a similarly large set of conditions and diseases.

Today, the implantable medical device market is driven by several major factors including the ever increasing elderly population and associated increase in the prevalence of chronic degenerative diseases. While many implantable medical devices are targeted to older patients, new developments also incorporate the needs of younger populations whose lifestyle and standard of living drive the lucrative cosmetic implant market. For the purpose of this perspective article, the focus will be on implantable devices with electrical features and function which may or may not require active electrical power to operate. Examples include implantable pacemakers, cochlear implants, drug infusion pumps, pressure sensors, and stimulators. Such devices either deliver

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therapy or provide monitoring of physiological parameters relevant to a particular medical condition. Special emphasis will be given to implants involving the use of microtechnologies and microelectromechanical systems (MEMS).

Many medical implants now incorporate microfabricated components or are entirely microfabricated. These include devices that have been approved and are designated as investigational. Pacemakers and cardiovascular defibrillators have recently incorporated MEMS accelerometers to sense body position and movement. The first Food and Drug Administration (FDA)-approved MEMS implant is the EndoSure® AAA Wireless Pressure Measurement System (Fig. 1) from CardioMEMS, Inc. This implantable sensor is placed in an aneurysm and monitors intrasac pressure during endovascular abdominal aortic aneurysm repair.⁵ Similarly, ISSYS Sensing Systems, Inc. is developing wireless microfabricated pressure sensors for managing congestive heart failure, pulmonary edema, hydrocephalus, and brain trauma. Their Titan Wireless Implantable Hemodynamic Monitor system (IHM) monitors pressure in the left atrium or ventricle and is currently in clinical trials.⁶

The purpose of this article is to introduce the multifaceted implantable medical device ecosystem and discuss some of the related challenges faced in the process of developing new implantable devices that leverage the advantages of microtechnologies. Specifically, the highly regulated nature of the implantable device market imposes unique engineering and translational challenges. This article also introduces new trends in implantable devices and highlights opportunities for future innovations that can impact the device-mediated medical treatment of various diseases and conditions.

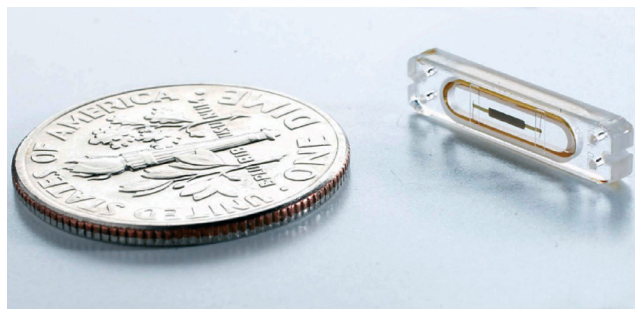


Fig. 1 The wireless microelectromechanical systems pressure sensor marketed by CardioMEMS, Inc. is part of the EndoSure® AAA Wireless Pressure Measurement System. The hermetically sealed sensor is deployed by a catheter into an abdominal aortic aneurysm during the repair of a thoracic aortic aneurysm via stent graft. The wire attached to the sensor (not shown) secures it to the vessel wall without the use of sutures. The sensor monitors intrasac pressure and detects intraoperative leaks of the stent graft. An external electronics module, the other major component of the measurement system, is placed nearby the implant to wirelessly power and read the sensor. Changes in intrasac pressure are transduced by a membrane which in turn changes the resonant frequency of the sensor (Image rights by IntelFreePress, Creative Commons Public License).

The implantable device ecosystem

The medical implant ecosystem is particularly complex in part due to the involvement of many stakeholders with differing motivations and requirements. Typically, this group consists of the inventor, patient, physician, healthcare provider, payer, regulator, and investor. Each stakeholder plays a role in determining the ultimate fate of inventions related to implants and how far down the path to commercialization they can proceed.

The ecosystem and environment around the development of implantable medical devices and medical devices has evolved since the 1960's and 1970's when cooperative efforts between industry, academia, and the medical community resulted in many of the implantable devices that are widespread today. Today, large medical device companies, pressured by the need to realize near-term payoffs, are focused primarily on introducing products that provide incremental improvement over previous iterations. Innovation in the form of new and disruptive technologies largely originates in start-ups, academic laboratories, and clinical research environments. In some cases, large companies are able to achieve innovation through the acquisition of small companies that have demonstrated compelling clinical data supporting the use of their implantable device and, in doing so, have assumed most of the risk and cost associated with the development of the new technology. Recently, St. Jude Medical, Inc., a leading and global medical device company, announced that it would acquire CardioMEMS in 2014.

In many cases, medical implant innovations originate in academic laboratories which have the freedom to explore new high risk concepts. For example, implantable devices being pursued by CardioMEMS, Second Sight (retinal prosthesis), and MicroCHIPS (drug delivery device) can be traced back to academic inventions by researchers. Academic environments can promote close interaction between clinicians actively seeking new solutions to urgent unmet medical needs and engineering faculty with know-how. The cross fertilization of ideas can lead to new inventions and start-up companies seeded by research activities that demonstrate early stage proof of concept of a novel implant solution. However, despite the environmental benefits and the willingness and freedom to try high risk, high reward projects, there are many imposing challenges that must be overcome when developing medical implants in academic environments including sustained funding, multi-investigator collaborations, and lack of knowledge and experience on successfully translating early stage inventions from the lab to the marketplace. Also, not all academic investigators are interested in pursuing translation of their inventions. The pressure to "publish or perish" may lead to abandonment of intellectual property protection. All of these factors contribute to the potential abandonment of promising technologies within academic laboratories.

A few select efforts originating in academic institutions have been successfully introduced to industry. These

innovative new implants are often championed by small start-up companies which face many challenges in crossing the “valley of death” between invention in the laboratory and introduction to the market. Early stage investment in medical devices traditionally sought by start-ups has declined recently due to uncertainty in the regulatory approval environment for new devices, the focus on short term pay offs, and changing health care laws (the Medical Device Tax Act took effect January 1, 2013 and charges a 2.3% tax on revenues for sales of medical devices). The medical device sector has experienced continuing declines in early stage venture capital investment,⁷ down by more than 40% since 2007 according to PricewaterhouseCoopers and National Venture Capital Association.⁸ Instead, substantial investments now occur at the later stages of development (*i.e.* after clinical validation and regulatory approvals) assuming that the clinical need and the market size are substantial.⁹ Despite this decline and the expected continued decline in 2014, the medical device section is still fourth in investment volume with respect to other industries.

Regulation of implantable devices

The FDA regulates medical devices in the US, the largest medical device market in the world, based on the definition laid out in section 201(h) of the Federal Food Drug & Cosmetic (FD&C) Act. Overall, medical devices are divided into three categories based on function and degree of risk; implantable electronic devices are largely designated as Class III since they typically provide life-sustaining function and therefore pose the highest risk to health in the event of failure (out of Class I, II, and III with Class I devices posing the least risk). Implants, such as knee and hip joint replacements, are Class II implants as they are not considered life sustaining. A device's class designation determines the appropriate regulatory pathway to gain federal clearance for the device to be marketed in the US. Class III devices, which typically take the premarket approval (PMA) route, are subjected to the most stringent controls and regulations; these implants must be shown to be both safe for use and effective in their intended clinical utility.

Class III is not universally applied to electronic medical implants. New devices can receive a Class II designation if shown to be similar to an existing approved device (predicate) within the class (Premarket Notification or 510(k) clearance) or by going through the *De Novo* classification process introduced by the Food and Drug Administration Safety and Innovation Act (FDASIA) introduced on July 9, 2012.¹⁰ For example, in 2005, the NeuroPort® Cortical Microelectrode Array received a 510(k) clearance for acute inpatient recording and monitoring of electrophysiological brain activity (Fig. 2; clearance originally received by Cyberkinetics Neurotechnology Systems, Inc. and now acquired by BrainGate™ Co.). The EndoSure® AAA Wireless Pressure Measurement System was reclassified as Class II from Class III in 2005 using the *De Novo* process.⁵ Similarly, the ingestible sensor from Proteus Digital Health also obtained a Class II designation through the *De Novo* process.¹¹ Proteus targets the difficult issue of patient adherence

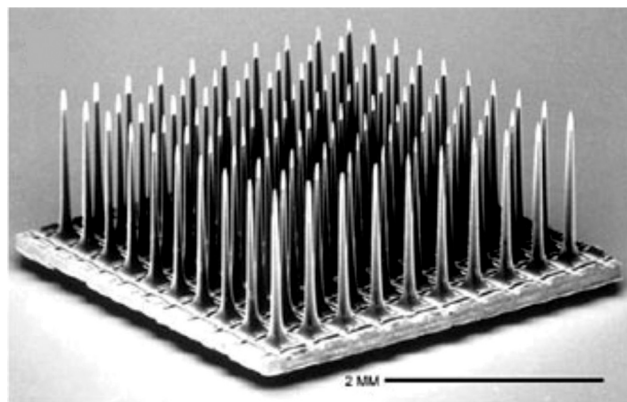


Fig. 2 The NeuroPort® is a 100 site intracortical silicon electrode array of 400 mm spacing. The array is inserted such that the silicon base sits on the surface and the electrode tips penetrate 1–2 mm of the brain. These electrodes provide the tissue interface in a brain-machine interface system. In the BrainGate™ system, the array is connected by a wire bundle to a transcutaneous port sitting on the skull which provides connections to an external decoder. The decoder can then be attached to a prosthetic limb or other assistive devices. In an on-going clinical trial, the feasibility of the system for decoding thoughts of paralyzed patients to control assistive devices is being investigated (reprinted with permission from ref. 3 © Nature Publishing Group 2002).

to pharmaceutical therapy by monitoring both the identity and timing of pill ingestion using a tiny wireless sensor integrated with the pill. The sensor was approved for use with placebo pills in 2012 and Proteus is pursuing approval for integration with pharmaceutical drugs. The burden to show both safety and efficacy necessitates significant development cost and time for medical implants to reach the market from the time of the initial invention (Fig. 3).

There is an alternative humanitarian use device (HUD) regulatory pathway for devices addressing rare and orphan conditions that affect or manifest in fewer than 4000 patients

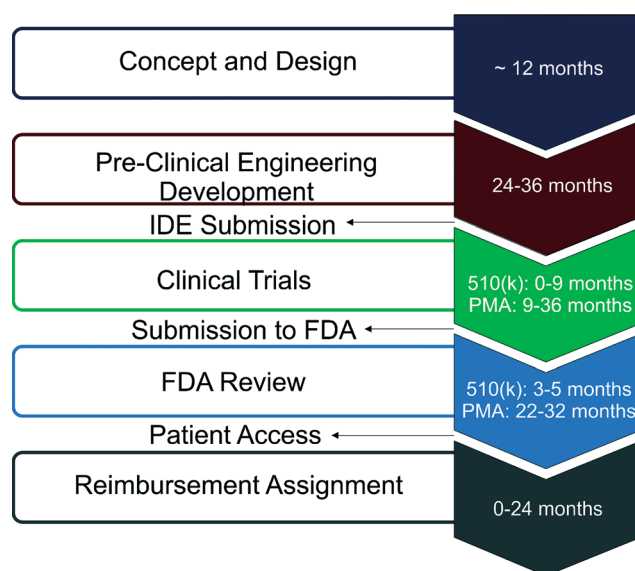


Fig. 3 Schematic on regulatory approval process steps and associated (approximate) timeline (modified from ref. 1).

per year.¹² Instead of requiring both safety and efficacy, the FDA requires demonstration of safety and probable clinical benefit. The first step is a HUD designation from the FDA. Typically for implants, a simplified investigational device exemption (IDE) is filed followed by a humanitarian device exemption (HDE).¹³ Unlike standard devices, current legislation requires that healthcare providers implanting HUDs possess institutional review board (IRB approval). One example of an implant recently approved through the HDE process is the Argus® II Retinal Prosthesis System (Fig. 4; Second Sight Medical Products, Inc.) which provides electrical stimulation to ganglion cells in the retina *via* an array of microfabricated electrodes to induce visual perception in blind retinitis pigmentosa patients.¹⁴

To acquire sufficient evidence for safety and efficacy, the FDA will require non-clinical data (related to biocompatibility, toxicology, immunology, stress, wear, *etc.*) as well as preclinical and clinical studies. Successful completion of preclinical studies will enable clinical trials in humans. At this point, both IRB¹⁵ and FDA approval are required before allowing clinical trials to commence. The IRB is a local ethical review board that reviews, approves, and monitors biomedical research involving humans such that the rights and welfare of the research subjects is protected. FDA approval is sought by filing of an IDE and regulatory review.¹⁶ At the conclusion of the typically multiple clinical trial phases, a final regulatory review occurs with the goal of achieving regulatory approval. For a more thorough discussion of medical device development, the reader is referred to ref. 17.

A few microfabricated devices have been used as investigational devices in humans, partly due to the significant and lengthy testing required to reach clinical trials. For example, since the first academic publication in 1999 reporting the initial device concept,¹⁸ the reservoir-based drug delivery device (Fig. 5) from MicroCHIPS reported the first successful human



Fig. 5 In the MicroCHIPS device, the drug is contained in an array of hermetically sealed reservoirs etched into a microchip that is implanted in the body. A wireless signal transmitted to the device activates the selected reservoir(s) and uses the application of electric current to melt the sealing membrane. This electrothermal release mechanism applies a discrete drug dose into the body. Repeated activation initiates sequential dosing in an on-demand manner. The microchip is housed in a titanium case such that it is exposed to the body while the supporting electronics are protected (reprinted with permission from ref. 2 © American Chemical Society 2013).

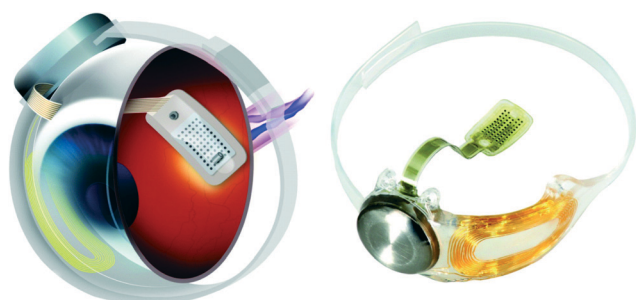


Fig. 4 Implanted portion of the Argus® II Retinal Prosthesis System. The system also includes glasses with an integrated camera and external electronics (not shown). The camera captures visual information which is processed and transmitted to activate specific electrode sites within the implant. Electrical stimulation of the ganglion cells within the retina results in visual perception. Left: three dimensional illustration of the implant with respect to the treated eye showing the placement of the electrode array directly on the surface of the retina. A retinal tack secures the array to the surface. Right: photograph of the electrode array, hermetically sealed electronics, and bi-directional communication coil (Images courtesy of Second Sight Medical Products, Inc.).

clinical trial using a wireless version of their implantable microchip device in early 2012. Teriparatide was delivered subcutaneously from a titanium encased implant using an exposed microchip to postmenopausal osteoporotic patients to increase bone mass.^{19,20} The expected filing for regulatory approval will be in 2014.²¹

Engineering considerations and challenges

The regulatory clearance process and the burden to demonstrate safety and efficacy play an important role in the engineering of the implant at several time points. We first discuss engineering concerns related to materials and components and then bring these into context by briefly reviewing the process to generate evidence to satisfy regulatory clearance requirements.

Typically, following the conception and invention stage, a prototype design is demonstrated. The importance of selecting appropriate materials for implants, even starting at

the proof-of-concept stage, cannot be overstated. Materials should be selected so as to provide the necessary electrical or mechanical function and avoid unwanted toxicity, acute or chronic inflammation, protein fouling, adverse reactions (allergies), infections, and premature mechanical failure. The tissue-device interface also needs to be carefully considered for effective function of the implant; the eventual formation of a fibrous tissue capsule arising from the body's immune response may not be acceptable if close contact or access to local tissues is required. Unfortunately, the selection of materials is often informed by incomplete biocompatibility data available from the manufacturer and the research literature.

The difficulty in selecting appropriate materials persists despite the long history of use of implantable materials; in 3000 B.C., the Incas used gold and silver in an ancient cranial surgery technique known as trephination. Historically, the use of synthetic materials in implants gained popularity in the 1940's. Many classes of materials are found in implants today including metals (e.g. cobalt–chromium (Vitallium), titanium, iridium, platinum), calcium ceramics (e.g. hydroxyapatite), glasses, and polymers (e.g. silicone rubber, Parylene, polyester, polytetrafluoroethylene, nylon, polymethylmethacrylate).²² Of these materials, several are commonly used in microfabricated components and systems.

Caution should be exercised in the use of conveniently available materials compatible with microfabrication for the purpose of generating prototype devices. Data acquired with such prototypes are not likely admissible for demonstrating safety and efficacy for regulatory approval. This adds additional cost and potential delays to an already difficult path to repeat critical proof-of-concept experiments in an appropriate material set. SU-8 is a popular microfabrication material used in the microdevice community and is frequently used in the development of implantable microdevices. Many researchers claim biocompatibility of SU-8 based on incomplete biological testing done by academic laboratories that is available in the published literature. However, the manufacturer explicitly cautions against the use of the material in implantable medical devices.²³ It should be noted that there are no known FDA-approved implants that utilize SU-8.

It is important to note that the FDA does not approve materials for use in implants – the FDA approves medical devices. An alternative approach is to select materials found in FDA-approved implantable devices. However, this approach may not guarantee success in demonstrating the safety of the implant. In particular, the processing techniques used on a particular material may result in toxic leachable products and thereby render it unsuitable for use in the implant. As an example, only specific formulations of silicone rubber are suitable for implant. Sylgard 184 silicone rubber (Dow Corning) which is commonly used in the microfabrication community is not a medical grade silicone rubber whereas Silastic® MDX4-4210 is a biomedical grade elastomer (Class VI United States Pharmacopeia (USP) polymer)²⁴ and may be a suitable alternative in some applications. Regardless of the material chosen, all implants will undergo biocompatibility and toxicity testing per

the standards set forth in the ISO 10993,²⁰ typically conducted by an established toxicology laboratory service following Good Laboratory Practices (GLP) guidelines. This includes an extensive battery of both *in vitro* and *in vivo* studies that determine safety. Most academic research efforts do not have the funding for such 'non-academic' studies and this necessary step in the regulatory pathway is often left to start-ups and other industry partners.

The response of materials to sterilization processes should also be considered. Sterilization is necessary to eliminate the presence of any microbiological organisms prior to implantation. Common methods used for sterilization involve the application of heat, chemicals, irradiation, or high pressure which may adversely interact with materials and compromise their properties.

Materials also play an important role in providing protection of electronic components from the corrosive saline environment of the body. Although there is no perfectly hermetic material, the packaging of devices including electronics is usually accomplished using metals, glasses, and ceramics which all possess low permeability. Polymers may also be appropriate as the primary packaging material in implants when hermeticity is not required or only required for shorter durations.

Medical implants with incorporated electronics typically require power. Despite miniaturization efforts, batteries are still large in comparison to microfabricated components and can significantly increase the overall implant size and weight. Batteries have a limited lifetime and may pose risk to the patient if leakage or malfunctions occur.²⁵ Wireless powering of medical implants can eliminate the battery and thereby reduce the implant size and the operational lifetime. The trade-off is that an external power system is required. Regardless of whether batteries or wireless technology is used to power the device, additional circuitry is required that must be hermetically sealed.

Once a near-final implant design has completed extensive testing at the benchtop and is suitably packaged, initial pre-clinical studies in normal animals or animal models may be initiated and can take place in academic environments with strategic collaborations between experienced animal researchers, clinicians, and engineers. The engineering effort is tracked as part of the regulatory clearance process by putting a device history file (DHF) in place to facilitate preclinical device development.²⁶ DHF is intended to ensure a well-documented device development process to achieve effective product design for intended use. Aspects of DHF include design inputs, design outputs, failure mode and error analysis (FMEA), verification, and validation. The preclinical development stage may include studies involving sterilization, biocompatibility, packaging, benchtop testing, and *in vivo* animal testing. The data generated will demonstrate safety and efficacy necessary to initiate the next phase involving human clinical trials. The final implant used in these trials will need to be manufactured following quality systems known as Current Good Manufacturing Processes (CGMP) as required by the Federal Food, Drug, and Cosmetic Act.²⁷

Barriers to translation

In addition to regulatory and engineering hurdles, innovative medical implants face other obstacles in the translational pathway to the marketplace. Many academic implant inventions are seeded initially by small research grants that result in production of the first prototypes or proof-of-concept components of what will ultimately be a much larger system. Early studies often focus only on demonstrating performance, usually in a pristine model environment not at all similar to the complex implant environment. Implants are typically complex systems involving multiple components that account for packaging, power, data, wireless communication, electromagnetic interference and safety, biocompatibility, sterilization, surgical procedure, and magnetic resonance imaging (MRI) compatibility. A single investigator may not possess the expertise or the necessary equipment and facilities required to address all of these requirements. Also, from an engineering perspective, decisions made by researchers at this early stage can have a profound impact on the future translation of the invention. For example, as discussed previously, researchers may select materials commonly used in research-grade devices but that are not appropriate in an implantable device.

Sustained funding of implant technologies in academic laboratories beyond initial proof-of-concept remains difficult, especially in the current federal and foundation funding environment. Federal grants are largely focused on continued innovation with the promise of a continuous stream of high impact journal publications on innovative new ideas. Therefore, it is difficult to garner the necessary continuous funding through conventional programs for advancing implant technologies. This is further exacerbated by the fact that implantable devices are often complex, multi-component systems requiring substantial funding and longer research durations in comparison to other biomedical technologies.

There has been some progress to prevent funding lapses and therefore the abandonment of promising new technologies in the lab. The introduction of new federal and foundation funding programs have allowed academic institutions to have a larger role in translation and innovation in the medical device space. For example, the National Institutes of Health (NIH) now supports translational research centers through its National Center for Advancing Translational Sciences (NCATS) program established in 2011 to speed the delivery of new cures and treatments to patients. The National Science Foundation (NSF) has similar programs through their Division of Industrial Innovation and Partnerships, such as Innovation Corps (I-Corps) which takes one step further and includes commercialization training through a boot camp-like approach. In addition, the program offers small grants to NSF-funded researchers to accelerate the translation of technologies. The Wallace H. Coulter Foundation supports Coulter Translational Partnership programs which move projects involving close collaboration of both biomedical engineers and clinicians to clinical application.

Many of these programs encourage the creation of start-up companies or the out-licensing of intellectual property to large established medical device companies to further advance technologies beyond the lab.

In order to ensure future translation of innovative implants, academic and industry inventors must seek early patent protection from their technology transfer offices. Most academic technology transfer operations in the US have limited resources and must make a decision on whether or not the intellectual property generated by the inventor will have a financial value substantial enough to offset patent prosecution fees and to generate licensing revenue. Start-up companies face a similar challenge and have limited financial resources to pursue patent filing and prosecution. This is further complicated by the need to secure access to several patents in order to ensure freedom to operate in a particular medical implant space. A natural bottleneck that arises preventing rapid technology development is that the required intellectual property may be widely distributed among many institutions or companies.⁹ The cost associated with licensing these required patents may be a significant barrier to a fledgling start-up effort.

Emerging trends in implantable devices

Medical implants in the future will likely combine both monitoring and therapy such that both modalities work together to achieve optimized and personalized closed-loop therapy that is informed by the patient's need.²⁸ This is not a new concept; cardiovascular implants with the ability to sense physiological parameters and provide timely electrical stimulation pulses were developed decades ago. However, the majority of medical implants are still largely open-loop. There has been recent progress in the development of closed-loop therapies for neurostimulation applications.

In the fall of 2013, the FDA approved the RNS® responsive neurostimulator from Neuropace, Inc. intended for the treatment of medically refractory epilepsy and it is the first closed-loop implant in the neurostimulator space.²⁹ This neurostimulator system includes both implanted and external parts that interface through wireless telemetry to allow programming and access to patient data. The implanted portion of the system detects abnormal electrical activity and intervenes to prevent seizure symptoms by applying an appropriate electrical stimulus that restores normal activity.

Depending on the type of implant and the sensors that are incorporated, there are also two levels of data transfer relevant to medical implants. The first is short-range communication between an external controller and the device, to monitor device status and performance and send commands to adjust operation. The second is remote monitoring, through data transfer between the device and an internet-based network. Remote monitoring of clinical events and symptoms reduces the frequency of routine follow-up visits. This in turn reduces staff time and costs while improving the

patient's quality of life.³⁰ Implantable wireless devices are therefore expected to play a growing role in the digital and wireless health revolution.

It is essential that medical implant development includes stringent tests and experiments to identify possible harmful effects of the wireless implant on the body and the body on the device.³¹ There are also vulnerabilities in device security that need to be considered. Wireless communications open the door to possible tampering or information theft. Devices triggered by a wireless cue can allow an unauthorized user to cause harm to the patient by sending commands that alter the prescribed operation. Besides intentional tampering, there is also the issue of an accidental device compromise due to interference from surrounding wireless communication. It is the responsibility of developers of wireless implantable devices to implement security measures to protect the device from intentional and unintentional tampering.

Another emerging trend is the emphasis on affordable implant technologies. This is driven by cost pressures from health economic considerations for reimbursement. This leads to a strong demand for implants that require surgical procedures that are more minimally invasive and offer shorter and less-costly patient recovery. With the increasingly difficult US market environment for medical device innovation, there is now increased attention on commercial development of medical implants intended for global markets where pricing pressures dictate technology adoption and market penetration.³²

Conclusion

Overall, the use of microtechnologies and MEMS in implantable devices is still in its infancy with few technologies currently approved for marketing in the US. The miniature form factor and wireless operation capability of microdevices offer technological advantages over traditional technologies. However, the developmental pathway for medical implants, regardless of size, remains long and challenging as a result of the uncertain regulatory environment and challenges in medical device funding from both federal and private sources. Even so, continued interest in the development of microtechnology-based implants is expected, driven by the increasing demand for implants in the ever increasing age portion of the world population and emphasis on personalized medicine that can be enabled by responsive, closed-loop implantable therapeutic devices.

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