SurFACTS in Biomaterials

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World's First Bioabsorbable and Infection-Reducing Antibiotic Screw Coming to Operating Theaters

The Finnish biotechnology company Bioretec Ltd. obtained the CE mark and sales permit in EU countries in September for its bioabsorbable antibiotic-releasing screw used in operating theaters. The novel implant helps reduce infections and the need for reoperations on bone fracture patients.

The antibiotic-releasing CiproScrew™ implant solves a significant medical challenge: it fixes and supports the bone during healing while precisely and safely releasing an antibiotic locally to prevent infections.

The antibiotic-releasing screw is used to treat, for example, complicated fractures, osteotomies, and arthrodeses and in the fixation of bone fractures in patients when infection is a potential risk. Advanced age and illnesses such as diabetes, rheumatoid arthritis, osteoporosis and alcoholism increase the risk of infection. Trauma surgery patients are particularly prone to serious infections arising from bone fracture fixation.

Turku University Hospital has conducted clinical research on the CiproScrew™ implant. Professor Hannu T. Aro of Turku University Hospital has performed ankle fracture fixations using the antibiotic-releasing screw.

"The new antibiotic-releasing screw works well in the treatment of these difficult injuries, and it is as effective as metal screws. Should

Bioabsorbable Screw Continued on Page 4

From the Editor

It is an exciting time in the medical materials industry, and for surface analysis and microscopy, since both areas are impacted by economics and politics.

In this issue is more on the continuing saga of the FDA's redesign of the 510(k). This is, of course, a critical issue for our industry as it can greatly alter the time-to-market and the associated costs for the commercialization of new medical devices.

This issue shows some exciting new products, changes in leadership, and several interesting new technologies in development. Thus while the economy remains poor, it does seems to be recovering.

Once again the small business innovation (SBIR) program has been funded, and once again only by continuing resolution. The program will now continue until May 31, 2011, so once more the long-term outlook is uncertain. Moreover, the funding levels for this critical program that creates small technology businesses remains stagnant. The Senate voted to substantially increase the program budget at the close of 2010, but unfortunately end-of-term and end-of-

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From the Editor
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By Steven L. Goodman, Ph.D., 10H Technology Corporation

year politics got in the way so that this reauthorization bill died in the House at the end of December. Hopefully, a reauthorization of this program will occur before the end of May with similar terms as the bill that failed at the end of 2010.

Finally, on the bright front, advances in instrumentation and biomaterials analysis continue to be very exciting. Some highlights include multiple new instruments that push the boundaries of nano-scale resolution. Here are some examples:

- Anasys Instruments has introduced the nanoIR that breaks the optical diffraction limit to enable nanoscale IR analysis of materials, as was briefly introduced by Khoren Sahagian at the 2010 BioInterface meeting. This instrument combines AFM and scanning IR excitation to detect molecular vibrations that enables mapping of chemical composition simultaneously with nanoscale topographic, mechanical, and thermal analysis.
- Fluorescence microscopy also has broken the optical diffraction limit with techniques that can achieve 50 nm resolutions. This is 5X better than the usually cited diffraction limit of 250 nm. This microscopy uses several variations on the theme of "stimulate emission depletion" or STED microscopy. While this has been shown to be possible for about a decade, this instrumentation is now being commercialized by Leica and in somewhat different forms by other microscope instrument firms. Someday these instruments may be as commonplace as confocals.
- Another nano-imaging technology was presented at BioInterface 2010 meeting by John Notte of Carl Zeiss. This instrument is the scanning helium ion microscope. It is much like an SEM, but instead of imaging with electrons it uses helium ions. This provides significantly better surface sensitivity than even low-voltage SEM, while also improving atomic number contrast and spatial resolution on especially low conductivity samples.

So, while we have the difficult politics of medical devices and still difficult economic times, at least we have wonderful new instruments we can use to develop our medical technologies. Now, if only we could afford them.

SurFACTS in Biomaterials is the official publication of the foundation and is dedicated to serving industrial engineers, research scientists, and academicians working in the field of biomaterials, biomedical devices, or diagnostic research.

The FDA's 510(k) Redesign Saga, Continued

By Phil Triolo, PhD, RAC, President, Phil Triolo and Associates, LC

The FDA is currently reviewing and revising the process it uses to allow the marketing of medium-risk devices in the United States. This premarket notification or "510(k)" process requires that a manufacturer establish that a device it plans to market in the US is "substantially equivalent" to another device currently marketed in the US for the same intended purpose(s). The FDA announced its program for revision of 510(k) requirements in a video conference in February, 2009 and, since then, held three "Town Hall" meetings where US stakeholders were able to express their concerns with the 510(k) process and FDA-proposed changes. A summary of some of the comments made at, and in response to, the first Town Hall meeting that was held in Minneapolis in May appeared in the May-June issue of SurFACTS.

Since that time, the FDA published a series of reports outlining numerous areas where it believes specific changes could be made to the process; and MDMA (Medical Device Manufacturers Association) and NVCA (National Venture Capital Association) jointly published the results of a survey of US manufacturers they sponsored that assessed the impact of the FDA regulatory process on US medical technology innovation. The results of the survey were less than complimentary of the FDA 510(k) and PMA review processes and drew an angry response from FDA Commissioner Shuren, reported in MassDevice.

Anyone interested in the potential changes that the FDA contemplates implementing to improve agency transparency, responsiveness, efficiency, and predictability with respect to 510(k) reviews is strongly encouraged to read through the reports published by the FDA. Among the more interesting suggestions is one recommending the establishment of a Class IIb product category. The latest update to the 510(k) redesign process that outlines the timelines for the implementation of any revisions can be found at www.fda.gov.

This SurFACTS article specifically addresses the survey findings reported in the MDMA/NVCA report authored by Dr. Josh Makower, a Consulting Professor of Medicine at Stanford, CEO of Exploramed Development LLC, and a venture partner at New Enterprise Associates, one of the largest US Venture firms; Aabed Meer, an MD-MBA candidate at Stanford University; and Lyn Denend, a Research Associate at Stanford. The report summarizes responses from 204 unique companies, which, according to its authors, represents approximately 20 percent of all public and venture-backed medical device manufacturers in the US that are "focused on bringing innovative new technologies to market to improve the public health (e.g., devices used to treat hypertension, obesity)."

The survey was designed to gather information on the resources (time, money) required to bring a new device to the US market via the 510(k) process and compare these with resources required to gain the CE Mark to allow the identical device to be marketed in the EU. The survey also assess the impressions of the interactions between industry representatives and regulatory personnel in the US and EU.

The findings are as follows:

In general, survey respondents viewed current U.S. regulatory processes for making products available to patients (the premarket process) as unpredictable and characterized by disruptions and delays. For example, 44 percent of participants indicated that part-way through the premarket regulatory process they experienced untimely changes in key personnel, including the lead reviewer and/or Branch chief responsible for the product's evaluation. A total of 34 percent of respondents also reported that appropriate FDA staff and/or physician advisors to the FDA were not present at key meetings between the FDA and the company. Factors such as these make the U.S. premarket regulatory process inefficient and resource intensive.

The above factors also contribute to significant delays in navigating FDA regulatory processes. Survey respondents reported that the premarket process for 510(k) pathway devices (of low- to moderate-risk) took an average of 10 months from first filing to clearance. For those who spoke with the FDA about conducting a clinical study for their low- to moderate- risk device before making a regulatory submission, the premarket process took an average of 31 months from first communication to being cleared to market the device.

510(k) Redesign Continued on Page 10

Bioabsorbable Screw Continued from Page 1

the antibiotic-releasing screw prove to be as successful in broader patient studies, future patients will no longer need to take antibiotics prior to their operation," says Professor Aro.

Developing a successful bioabsorbable product for use in an operating theater is an ambitious project. Bioretec's founder, Professor Pertti Törmälä, has 30 years' experience researching bioabsorbable materials.

"We have improved our manufacturing processes and machinery over the years. Improvements enable us to successfully combine two different material components The strength properties of the new antibiotic screw are based on Bioretec`s in-house developed process to create mechanically active polymer-material. Infection prevention is based on the combined broad-spectrum ciprofloxacin. The implant degrades in a controlled manner over the course of two years, releasing the antibiotic for about six months after the surgery," confirms Professor Pertti Törmälä.

The antibiotic screw can also help reduce costs in the health sector by preventing additional complications and renewal operations.

Scaling PEEK's Peaks

Invibio Biomaterial Solutions (West Conshohocken, PA) is investigating other physical characteristics that influence the biological response to polymers: topography and surface chemistry. Specializing in implantable PEEK-based products, the company is learning that there's more to a biomaterial than how it's used or what's in it. As PEEK materials begin to be employed in trauma devices, Invibio is investigating how manufacturing influences the material's surface texture, which affects its ability to prevent bacterial adhesion and decrease the risk of infection.

PEEK Optima rods from Invibio undergo surface texturing, enabling them to resist bacterial growth.

To determine PEEK's susceptibility to infection, Invibio commissioned the AO Research Institute (Davos, Switzerland), in collaboration with Aberystwyth University (Penglais, UK) and Cardiff University (UK), to compare PEEK's resistance to bacterial adhesion to that of titanium. "This study revealed that bacterial adhesion depends on both the adherent organism and the material surface," explains John Devine, Invibio's strategic development director.

Injection-molded PEEK, for example, is less susceptible to both S. epidermidis 138 and S. aureus V8189–94 colonization than machined PEEK, Devine says. In the case of S. epidermidis 138, the decreased bacterial adhesion to injection-molded PEEK is attributable to its smoother surface, while the adhesion of S. aureus to PEEK appears to be linked to the material's oxygen content, or surface chemistry. "S. epidermidis 138 adhesion to injection-molded PEEK is comparable to the 'gold standard' of orthopedics—titanium," Devine notes. "While less bacterial adhesion on a smoother surface has also been demonstrated in metals, polymeric materials offer greater scope to reduce bacterial adhesion through additives, surface modifications, and slow-release agents." Over the years, PEEK's biocompatible properties have enabled surgeons to use it in spinal applications such as interbody devices, semirigid posterior dynamic stabilization rods, and—most recently—vertebroplasty devices. "In addition, the material exhibits critical mechanical properties, including high strength, radiolucency, and a modulus comparable to that of native bone," Devine says. "Hence, it can be used as a mechanical spacer in cervical and lumbar fusion devices, offers wear resistance in self-mating applications such as cervical disks, and enables clear monitoring of the surgical site."

PEEK Optima rods from Invibio undergo surface texturing, enabling them to resist bacterial growth.

However, PEEK's use in other application fields presents new challenges. "The results of the tests performed to determine our material's resistance to bacterial growth illustrate that the biological response to PEEK can be tailored by the choice of manufacturing method," Devine concludes. "Different manufacturing methods result in different surface topographies, and different surface topographies can affect bacterial adhesion."

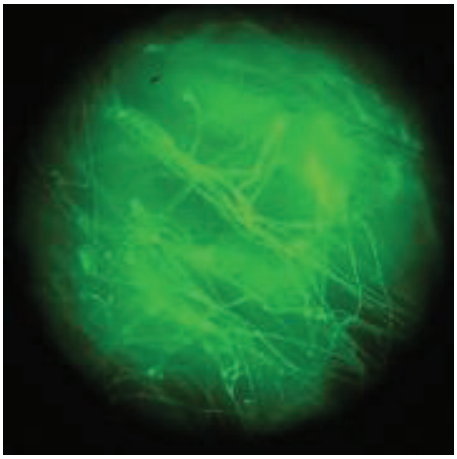
For Medical Applications, Two Silks Are Better than One

By Bob Michaels, Medical Product Manufacturing News

From marshaling bacteria to grow silk proteins to replicating silk produced by honeybee larvae, the manipulation of natural silk has emerged as a promising approach for healing wounds, fabricating sutures, and repairing damaged tissue. Adding to the buzz is a team of researchers from academia and industry that has succeeded in genetically modifying silkworms so that they can spin spider silk. Their labors could lead to the development of a commercially viable native silkworm silk with the legendary strength of spider silk.

Although silkworms have been harvested for centuries, their native silk is too weak for many medical applications. In contrast, spider silk is stronger than steel and more flexible than Kevlar. However, it is not available in large quantities, nor is there an economically viable means for purifying it so that it can be polymerized and spun into strands.

Facing this conundrum, Kim Thompson, CEO of Kraig Biocraft Laboratories Inc. (Lansing, MI), asked Malcolm Fraser, a professor of molecular biology and genetics of viruses at the University of Notre Dame (Notre Dame, IN), whether silkworms could be used to purify and polymerize spider silk. "That was a 'Yeah, sure,' moment for me," Fraser recounts. "Silkworms are effectively a protein bioreactor platform. You can make virtually any protein of choice in the silkworm, or you can modify the silk itself to have whatever properties you would like." The key to producing this transgenic



A green fluorescent protein attached to spider silk protein demonstrates that recombinant silkworm and spider silk is truly a composite structure.

silk is piggyBac, a sequence of DNA known as a transposon that can insert itself into the genetic machinery of a cell. "PiggyBac is a transposable element," explains Fraser, who holds a patent on this technology. "For several years, we've been defining its characteristics in terms of movement and its ability to be used as a gene vector to carry genes into the genome of many, many species."

While using piggyBac to engineer spider silk into silkworm silk, Fraser's team attached a green fluorescent protein to the spider silk protein to observe whether the two silks had chemically bonded. The success of this test convinced them that the resulting material was not simply silkworm silk with an admixture of nonintegrated spider silk. "It was actually a composite structure," Fraser adds.

The engineering of the additional sequence for encoding the green fluorescent protein also demonstrated that many other protein sequences could be added into the structure of the spider/silkworm composite silk. "Our vision is that some of the protein sequences that we can incorporate will be peptide hormones or growth factors that can stimulate the growth of particular kinds of cells and speed wound healing or reduce scar tissue formation during wound healing," Fraser says. For burn victims, he envisions making a silk-fiber mat that stimulates the growth of normal skin rather than scar tissue.

To convert the transgenic silk into medical products such as ligament scaffolds, however, manufacturers must be able to fabricate it in commercial quantities and manipulate it into threads with the appropriate diameters. "A lot of post-genetic-engineering manipulations will be needed," Fraser notes. "But since silkworm silks have already been used in some surgical applications, the FDA shouldn't have a big problem with the subtle modifications we're making. Thus, genetically modified silkworm silk should be easily available in five to seven years."

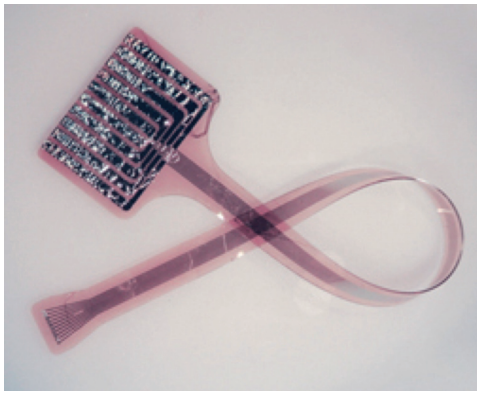
Bright Future Ahead for Flexible Diamond-Coated Electrode

By Shana Leonard, Medical Product Manufacturing News

Thanks to their customary use in engagement rings, diamonds have come to represent a lifelong commitment "'til death do us part." As researchers at Case Western Reserve University (Cleveland) are discovering, however, diamonds may provide a similarly long commitment in the body in the form of an implantable diamond-coated flexible electrode designed to last a lifetime.

"There are several very attractive engineering properties for the use of diamond as an electrode in general, and especially for an implantable electrode," says Heidi Martin, a professor of chemical engineering at Case Western leading the research. "If you're thinking of making an implant out of something that will last forever, that's very appealing because you don't want to do surgery several times because the material goes bad."

Deterioration of quality, performance, or physical structure of an implanted device over time is an ongoing problem, according to Martin. In the case of platinum electrodes used in neurostimulation, for example, data has shown material degradation and the presence of platinum chloride in nearby tissue, she says. Diamond, in contrast, is known for being chemically robust and stable; it won't corrode in the body over time.



An implantable diamond-coated flexible electrode is designed to last a lifetime in the body.

In addition to forming more-durable neurological electrodes, diamond demonstrates potential for improving sensing electrodes. Its basic electrochemical properties and wide operating range could enable the detection of chemicals that were previously undetectable. "For instance, we have some data that we can detect a specific neuromodulator that people couldn't see before because it oxidizes at too high of a potential for other electrodes to sense," Martin says. "The role of this neuromodulator could now be explored electrochemically."

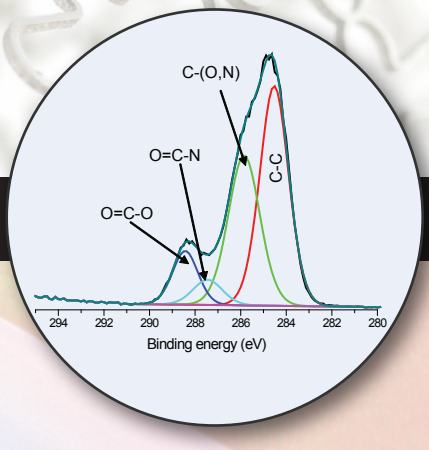
Diamond may also help overcome obstacles in chemical sensing. "One of the common interferences you get with biosensors is the presence of oxygen in the tissue," Martin adds. "[Conventional] metal electrodes will reduce the oxygen and create a signal that will interfere with whatever you're trying to measure." Because a diamond electrode greatly inhibits the electrochemical reduction of oxygen, it could minimize interference.

Despite these numerous biomedical benefits, the abrasive and tough nature of diamond does not lend itself to abundant use in applications requiring contact with the body's soft tissue. With this in mind, Martin and Chris Zorman, a professor of electrical engineering and computer science, are exploring a diamond-on-polymer electrode construction that capitalizes on only the desirable qualities of diamond by placing it solely at the biological interface.

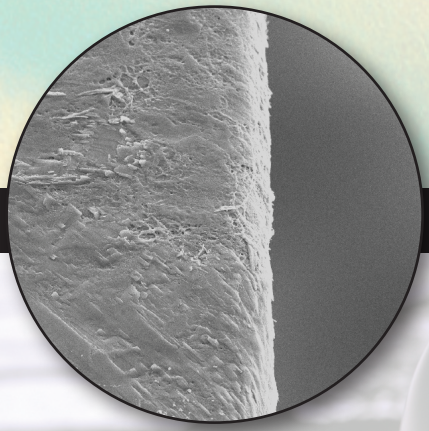
To achieve this design, the researchers grow diamond at extremely high temperatures—around 800° to 900°C—on a silicon-based substrate. They then configure the backplane of the electrode, the electrical contacts, and other components on top of the diamond. Once this step is completed at room temperature, the team releases the diamond film from the silicon substrate and transfers it to a polynorbornene (PNB) polymer, yielding an electrode that features diamond only at the desired interface.

Although the scientists are optimistic about the viability of the diamond-on-polymer electrode, they are still conducting fundamental research and optimizing the structure. Martin anticipates that they may be able to move into clinical trials in three to five years. "This particular architecture will allow us to make a diamond electrode that is truly implantable for long-term use," she says. "Consequently, the diamond electrode could be a superior long-term implant, replacing other carbon- or metal-based electrodes."

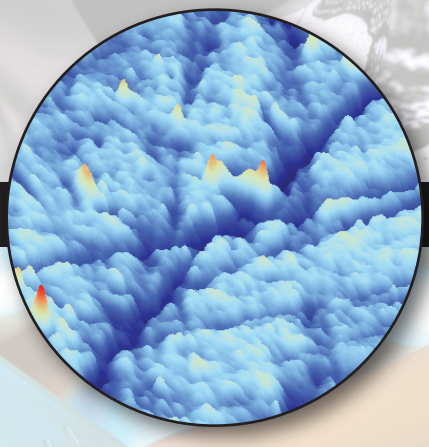
Specialists in Materials Characterization



XPS Spectrum of Hydrophilic Polymer Coating



SEM of Polymer Coated Stent



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Survey Reveals Cardiologist Preference for Bioabsorbable Stents Will Fuel Interventional Cardiology Market by 2013

According to a comprehensive global survey on stents, stent-grafts and vulnerable plaque by iData Research, the leading global authority in medical device and pharmaceutical market research, the majority of cardiologists in the U.S., Europe, China, India, Middle East and Africa would use a bioabsorbable stent for the treatment of coronary angioplasty. In contrast, the majority of cardiologist in Japan and Latin-America would not use a bioabsorbable stent.

A recent report released by iData Research on the interventional cardiology market revealed that bioabsorbable stents are expected to enter the European market by 2013 and the U.S. thereafter. The U.S. market is estimated to quickly reach almost $750 million with companies such as Abbott Laboratories, Biosensors International, and REVA Medical emerging as leaders.

iData's survey details the preferences and usage patterns from hundreds of cardiologists worldwide for bioabsorbable, bifurcated and drug-eluting stents, stent-grafts and vulnerable plaque treatment.

"The survey provided dramatic differences between geographical regions in usage trends," says Dr. Kamran Zamanian, CEO of iData. "Cardiologists in the U.S. and Europe are more willing to use new technologies such as bifurcated and bioabsorbable stents, while Japanese and Latin American cardiologists are more resistant, citing the lack of long-term clinical data, early recoil and technical challenges as drawbacks to these technologies."

iData's accompanying market report states that the U.S. market for interventional cardiology is expected to reach almost $5 billion by 2017, with increasing drug-eluting stent sales and the emergence of bioabsorbable and bifurcated stents fueling market growth.

iData's global cardiologist survey series includes: "Stents, Stent-Grafts and Vulnerable Plaque Treatment" and "Deep-Vein Thrombosis Treatment and Screening". These surveys accompany iData's newest global 3-report series on the "Markets for Interventional Cardiology Devices".

For more information, register free on iData's website at: www.idataresearch.net/idata/registration.php

Biocoat, Inc. Appoints New President

Keith Edwards has recently been appointed President of Biocoat, Inc. Horsham PA. The announcement was made by Biocoat's Chairman & CEO, Djoerd Hoekstra.

Biocoat is an R&D company specializing in biomaterials coatings for medical devices. The company's hydrophilic coatings are used by leading medical device companies worldwide, making today's advanced interventional procedures possible.

Keith comes to Biocoat from Biomet, Inc. a global leader in the manufacture of musculoskeletal products. At Biomet Keith held the position of Group/Senior Product Manager with responsibilities for the $120 million Bone Stimulation and Graft Material business segments. He is a graduate of Union College and attended New York Medical College.

Medtronic Presents One-Year Data on Endurant® Stent Graft

An implantable medical device used in the minimally invasive treatment of abdominal aortic aneurysms, the Endurant® Stent Graft System from Medtronic, Inc., delivered strong results through one year of patient follow-up in the company's U.S. pivotal study, according to clinical data presented at VEITHsymposium™. Approved by the U.S. Food and Drug Administration (FDA) under an investigational device exemption (IDE), the prospective study involved 150 patients at 26 U.S. medical centers and met its primary endpoints. In the study, the Endurant System was associated with no post-operative aneurysm ruptures or aneurysm-related mortalities at one year, and there were no mortalities from any cause at 30 days.

"The clinical results with Medtronic's Endurant Stent Graft System out to one year in this study are quite encouraging," said the study's principal investigator Dr. Michel Makaroun, M.D., professor and chief of vascular surgery for the University of Pittsburgh School of Medicine. "Based on this data, the Endurant Stent Graft, with its low-profile delivery system and accurate deployment, appears to be safe and effective in the short term. It will prove to be a great addition to the currently available devices in the management of abdominal aortic aneurysms for a wide range of patients."

The study's primary safety and effectiveness endpoints were major adverse events (MAE) at 30 days and a composite of technical and treatment success of the device at one year, respectively. Significantly for clinical practice, the study included patients with "landing zones," or healthy aortic neck lengths, as short as 10 mm, whereas most other trials of aortic stent grafts have required neck lengths of at least 15 mm.

The study monitored changes in aneurysm size and stent graft migration, a concern with current endovascular treatment. Nearly half (47.1 percent) of the aneurysm sacs that were treated with the Endurant Stent Graft System in the study decreased in size between one month and one year post-procedure, and none of the sacs increased in size; the rest (52.9 percent) remained stable in size during the same time period. In addition, none of the stent grafts migrated from their original placement.

The study also monitored the occurrence and type of endoleaks, which can result in persistent blood flow into the aneurysm sac. Through one year post-implant, there were no (zero) Type I or III endoleaks.

The Endurant Stent Graft System is currently used to treat patients with abdominal aortic aneurysms in approximately 100 countries around the world. The leading abdominal stent graft outside the United States, it received the CE (Conformité Européene) mark in July 2008. The Endurant System is an investigational device in the United States, where its clinical use is limited to studies approved by the FDA. It is currently under review by the FDA for pre-market approval (PMA).

Medtronic is committed to advancing the treatment of cardiovascular disease through collaboration with leading clinicians, researchers and scientists worldwide.

Now in its fourth decade, VEITHsymposium provides vascular surgeons, interventional radiologists, interventional cardiologists and other vascular specialists with a unique and exciting format to learn the most current information about what is new and important in the treatment of vascular disease.

510(k) Redesign Continued from Page 3

In contrast, respondents said it took them an average of 7 months in Europe from first communication to being able to market the same (or equivalent) device. For higher risk devices seeking premarket approvals (on the PMA pathway), responding companies indicated that it took an average of 54 months to work with the FDA from first communication to being approved to market the device. In Europe, it took an average of 11 months from first communication to approval.

Further, the respondents reported that the FDA compared unfavorably to European regulatory authorities in other areas:

- PREDICTABILITY – 85 percent of respondents considered EU authorities to be highly or mostly predictable, while only 22 percent gave the FDA the same ratings.
- REASONABLENESS – 91 percent of respondents rated EU authorities as highly or mostly reasonable compared to just 25 percent for the FDA.
- TRANSPARENCY – 85 percent found the processes and decisions of the EU authorities to be highly or mostly transparent compared to 27 percent for the FDA.
- OVERALL EXPERIENCE – 75 percent of respondents rated their regulatory experience in the EU excellent or very good. Only 16 percent gave the same ratings to the FDA.

With respect to costs to bring a new, innovative device to the marketplace, the report states the following:

The *survey data also showed that the average total cost for participants to bring a low- to moderate-risk 510(k) product from concept to clearance was approximately $31 million, with $24 million spent on FDA dependent and/or related activities. For a higher-risk PMA product, the average total cost from concept to approval was approximately $94 million, with $75 million spent on stages linked to the FDA. (These estimates do not include the cost of obtaining reimbursement or any sales/marketing-related activities.) Survey respondents confirmed that they are able to make their products available to patients faster and at a significantly lower cost in markets such as Europe. For U.S. companies, these mounting costs are unsustainable in a venture-backed industry where less than one out of four medtech startups succeed, 50 percent of all reported exits are less than $100 million, and the total pool of available investment capital is shrinking.*

Perhaps most importantly, the survey revealed that the suboptimal execution of FDA premarket regulatory processes has a significant, measureable cost to U.S. patients in the form of a device lag. Respondents reported that their devices were available to U.S. citizens an average of two full years later than patients in other countries, due to delays with the FDA and/or company decisions to pursue markets outside the U.S. before initiating time-consuming, expensive regulatory processes in their own country. In some cases, this device lag reached up to 70 months (nearly six years).

The results do not paint a very pretty picture of the regulatory climate for patients who may benefit from new technologies whose introduction to the US marketplace is delayed, or to manufacturers who plan to introduce an "innovative new" product to the marketplace. Further, the results, unfortunately, confirm many of the frustrations I, and my clients and colleagues, experience with the current 510(k) process. In particular, we have seen increases in questions concerning 510(k) "deficiencies" (requests for additional information) whose answers, when and if provided, cannot significantly improve the safety or effectiveness profile of a medical device. But they do significantly increase the resources required to clear the device for marketing.

My personal experience is that the "reasonableness" of reviews – which I measure by the relevance of identified "deficiencies" to the safety and efficacy/ performance of the device and to the justification of the request for additional information – appears to be more influenced by the branch of the FDA reviewing the 510(k) than by specific reviewers. Thus, the identical device used for different intended uses may gain rapid clearance when submitted to one branch, and take an extra six months to gain clearance for marketing for a different indicated patient population that requires submission to a different branch. The differences can be partially attributed to different risk profiles associated with the use of the same device for patients varying in their morbidity and medical need for treatment and the availability of alternative treatments; and/ or to the nature or overall philosophy/ approach of the branch as fostered by its Chief.

Dr. Shuren's response to the MMDMA/ NVCA report focused on two concerns.

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510(k) Redesign Continued from Page 10

First, that the sample size of responding companies was not significant enough from which to draw conclusions; and second, that the reason that the review period associated with launching a device in the US is so long is that the FDA is willing to meet with companies and discuss their submissions early in the regulatory process.

I, too, have my concerns with the report, especially with the way that costs are attributed to FDA-dependent and/ or related activities (FDA costs). The charts provided assign all product development costs incurred after the establishment of the feasibility of a new technology to FDA costs. This implies that the testing and design iteration necessary to reasonably demonstrate the safety and efficacy/ performance and substantial equivalence of an innovative new device is only completed in order to meet FDA requirements. Certainly, the resources required to document details of design and development activities, prepare documents and communicate with FDA officials, prepare and review an IDE and/ or 510(k), wait for their review, and respond to questions can be attributable to "regulatory" costs.

However, even if there were no regulatory agencies, good business practices, as well as a prudent risk assessment process, would dictate a rigorous, documented medical device development process that conforms to the intent, if not letter, of the FDA's Design Control regulations. Documentation of design inputs and outputs (specification development) and design verification and validation (product testing, including evaluation under real or simulated end-use conditions) would still be created. Review of the documentation by external regulatory personnel would not, however, be required.

Perhaps one way to reasonably parse the FDA costs assigned in the report into those that are regulatory or product-development related would be to separate the costs for materials and engineering personnel from the costs of regulatory and clinical personnel working on the product. Although there may be no clear method for separating these (regulatory versus development) costs, it is very clear, to me, at least, that identifying all development costs as regulatory expenses is not justifiable and suggests a bias in the report that unfavorably taints results that would speak loudly even if the FDA costs were half of those identified.

Another concern is with the way that the differences in review times for devices cleared in the US and CE Marked for marketing in the EU have been calculated. Most of the companies I work with launch their products in the US and then seek the CE Mark to allow marketing in the EU. The time to gain the CE Mark is always shorter than the time to gain FDA clearance. However, the two processes are not started at the same time, and the information required for the Technical File presented to the Notified Body (NB) for CE certification has been supplemented with information already provided to the FDA. That is, one reason that the review period for the CE Mark is shorter is that the data and reports that need to be in place have been refined and, in some cases, finalized before presentation to the NB. Yet, the time associated with refinement and finalization of documents counts toward FDA process time, not CE Mark process time.

I do not mean to suggest that the regulatory costs associated with bringing an innovative new device to the marketplace are low or necessarily acceptable, or that the time to review and clear an innovative new device for marketing a device in the US is shorter than it is to CE Mark the same device for sale in the EU. However, I would suggest that the FDA costs are lower, and the regulatory review time differences may be shorter between the US and the EU, than those reported.

Why are there such discrepancies in the impressions of interactions between FDA and NB personnel? My personal opinion is that the most important difference in reviews of the same devices by the FDA and NBs is in the experience of the reviewers with the specific devices under review. Most technical experts employed by NBs are hired because of their expertise and experience developing and evaluating the same types of devices they are asked to review. These technical experts are already aware of the major safety and efficacy issues associated with the devices and areas of technical concern. In contrast, FDA reviewers often have a more broad-based training in engineering, science, and clinical disciplines, but lesser direct experience in the specific devices they review. This lack of direct product experience, coupled with a conservative agency approach, leads to a cautious approach of reviewers and is associated with requests for information that may not contribute significantly to the assurance of the safety and efficacy/ performance of an innovative new device. This approach leads to drawn out review periods and, when questions remain unreasonable or unanswerable, to a degradation of interactions and impressions.

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510(k) Redesign Continued from Page 11

What to do?

I've obtained the most reasonable and predictable reviews from the FDA when I've conducted a pre-IDE meeting or held discussions with the Agency. It has not been easy to cajole clients to agree to or participate in these meetings. The most often cited reason for their reluctance to engage the agency in conversation or in a "pre-IDE" meeting before submitting a 510(k) is that it takes too long. A secondary reason is that the Agency has previously agreed to a documented approach discussed during the pre-IDE meeting, yet has changed its opinion/ position by the time the notification is submitted. Sometimes this is the result of a change in personnel. Other times it is a shift in the FDA's understanding of the risks and benefits associated with the device.

These client concerns are both legitimate. However, a short discussion with a reviewer to assure that the Agency's "current thoughts" on the information that needs to be provided to support claims of substantial equivalence/ reasonable assurance of safety and efficacy do not extend beyond those in the most recently published FDA guidance document can be time well-spent. I have found that provision of either a detailed protocol for evaluation of a new characteristic and/ or submission of verification and validation plans can form the basis of more substantial conversations, which some reviewers only agree to as part of a formal pre-IDE process.

Regardless of the approach, it appears that, at least until the FDA's review pendulum swings back into the "Least Burdensome," more reasonable zone, manufacturers should expect prolonged review periods for 510(k)s and unpredictable requests for additional information.

NOTE: Legislators have taken notice; 15 US Senators recently sent a letter to FDA Commissioner Hamburg to adopt a more deliberate and cautious approach to amending the 510(k) than that outlined by the FDA.

Terry Schlotterback, Ex-Zimmer Executive, Joins Affinergy Board of Directors

Affinergy announced today that Terry Schlotterback has joined its Board of Directors. Schlotterback spent 20 years with Zimmer, most recently in two key leadership roles as President of Zimmer Trauma Division and President of Zimmer Spine Division. Previously, he served as Vice President at Zimmer in Sales, Product Development, and Global Marketing Services roles as well as leadership roles at Depuy and Mitek Surgical Products, divisions of Johnson and Johnson. Affinergy develops medical devices for use in orthopedics, sports medicine, and general surgery.

"Affinergy's robust product pipeline and compelling vision for growth gives me great enthusiasm to actively support this drive to commercial success," said Mr. Schlotterback. "These products can improve patient outcomes while simultaneously containing healthcare costs. I am confident that surgeons will be eager to incorporate these proprietary products into their practices and distributors will find them to be valuable additions to their offerings."

"Terry has a unique combination of experiences across orthopedic markets as well as across functional areas such as product development, sales, and executive leadership," said Peyton Anderson, CEO of Affinergy. "He has already proven to be a tremendous advisor in terms of our product development and hiring plans for the Affinergy commercialization team. Terry's expertise and deep industry connections will be critical to our long term growth plans. On a personal level, Terry is a thoughtful mentor with impeccable integrity who is deeply committed to improving patient outcomes."

Mr. Schlotterback currently serves on the Board of Directors at Orthopediatrics which is developing specialized orthopedic products for children. He lives outside of Warsaw, Indiana.

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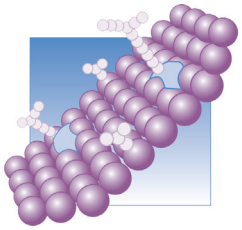

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