

SurFACTS in *Biomaterials*

May-June 2010 Volume 15 Issue 3

Reports from the FDA's Minneapolis "Town Hall" Meeting (and suggestions for changing the 510(k) process, if indeed, it must be changed...)

By Phil Triolo, Phil Triolo & Associates LC

As many of you are aware, the FDA is in the process of redesigning its premarket notification process for medical devices. Premarket Notifications, also known as "510(k)s," are submitted to the FDA to demonstrate that most manufacturer's medium-risk (Class II) and some low-risk (Class I) medical devices are "substantially equivalent" to predicate device(s) (primarily other devices already cleared for marketing in the US by the 510(k) process which are intended for the same use). If the FDA determines that the information in a 510(k) is adequate to establish that a new device is substantially equivalent to a predicate device, the FDA "clears" it for marketing. The process has been under scrutiny

for the past several years, as critics contend that, in some instances, the process does not adequately protect the public from the use of unsafe or ineffective medical devices.

The FDA held a public meeting in February 2010 during which time it announced that it plans to modify the 510(k) requirements and/or review process. (Note: Ralph Hall, Distinguished Professor and Practitioner of Law at the University of Minnesota Law School, characterized FDA's solutions as "ready, fire, aim" because there are no data showing a problem driving these solutions.)

This has led to concern amongst medical device manufacturers and the venture capital com-

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From the Editor

I really enjoy my work. Many of you know that I have a consulting and services business that provides analytical microscopy solutions to medical device and related industries such as biotechnology and pharma. I see my firm's mission is to provide clients with the best possible microscopy solutions for their R&D, quality assurance, regulatory, scientific publication and (sometimes) public relations needs. Regardless of the size of the client firm, we strive to provide clients with the most affordable methods and instruments for the problem at hand. I have had to direct clients away from purchasing or contracting for extremely expensive, high-end analytical instruments and methods for problems that are readily solved with much simpler and affordable methods such as optical light microscopy. Happily, this is rarely a problem since even the big guys appreciate saving money.

One of the things I like best about my work is keeping abreast of recent developments in analytical microscopy and related instrumentation. It is good that I enjoy this since this alone can be a nearly full time job. Keeping up with advances and new

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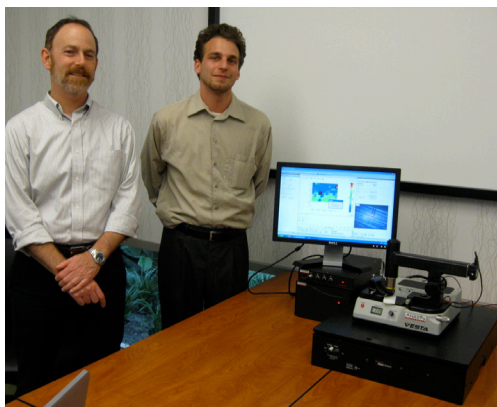
From the Editor Continued

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

instruments is necessary so that we can provide the best value to current and future clients. Last month, however, I was working with a client that was not a medical device firm seeking analytical solutions. Instead, this client was a relatively young company that had developed a new analytical instrument for which it is seeking applications. Working for instrumentation companies is not something my firm routinely does, but in this case I felt it was important due to the potential applications of this instrument for present and future clients, and the readers of *SurFACTS*. By working with this instrumentation company I was able to kill the proverbial two birds with one stone: learning about a new analytical instrument and providing value to current and future medical device clients.

The instrumentation client was Anasys Instruments Corporation of Santa Barbara, CA. (Yes, I had to travel from the Midwest to Santa Barbara in February. Sometimes I really enjoy my work.) This new instrument called the Vesta measures the in situ thermal transition properties of material surfaces, not bulk, with circa 100 nm spatial resolution. This provides nanoscale measurements of melting and glass transitions (T_m and T_g), as well as some local thermal mechanical property measurements. This is unlike any other analytical instrument. As this is not the place to advertise, I will limit my comments and discussion but instead direct you to the company's website if you have further interest: www.anasysinstruments.com/. There is a downloadable applications note that I co-authored with Anasys that demonstrates applications of the Vesta for orthopaedic bearing polyethylene, drug coated stents, contact lenses and some other medical devices at www.anasysinstruments.com/Medical_Devices.pdf.

For the week of May 24 I traveled with Khoren Sahagian of Anasys Instruments in the Minneapolis area to show the Vesta to multiple medical device firms. It was exciting to meet with dozens of scientists and engineers, discuss their analytical needs, see their devices and materials, and demonstrate how the Vesta could solve some of their materials analysis problems. In addition to meeting with individual companies, we also demonstrated the Vesta in a conference room at the University Enterprise Laboratories in St. Paul, MN. The UEL is a small business incubator with several medical device and other firms (www.uelmn.org/). The UEL is also home to Ewald Consulting, which is the management office of our Surfaces in Biomaterials Foundation. In between meetings and demonstrations of the Vesta to UEL firms, Janey Duntley, who works with me to put together *SurFACTS*, stopped by to record this. The photo shows Khoren (on the right) and me standing by the Vesta. It was a fun trip. I learned a lot, met with dozens of interesting persons developing exciting new products that save lives, saw many interesting analytical problems and perhaps solved a few, and enjoyed unusually warm weather in Minneapolis. I really enjoy my work.



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munity who fear that any changes will most probably result in a more complicated, burdensome, and time-consuming clearance process that will hinder the advancement of medical devices to the marketplace.

Already there is an apparent or at least industry-perceived shift in the review of new 510(k) applications. Review times are certainly longer than they were a few years ago. Whether or not this is the result of additional scrutiny of 510(k)s or a consequence of reviews being conducted by a rash of new reviewers is a matter of opinion. The FDA asserts that nothing has changed. I liken the situation to the actions that took place on interstate highways a decade or so ago. A group of motorists, to promote lower speeds on the interstate or greater fuel efficiency, would drive at the speed limit across all lanes of traffic. They fully obeyed the regulations in place at the time. There was no change in the speed limit and no laws were broken, yet traffic slowed considerably.

In order to gain stakeholder comments on the need for change as well as the form any change to the 510(k) process should take, the FDA held one of three planned "Town Hall" meetings in Minnesota last month. I was not in attendance. However, Joe Chinn was able to secure reports from the Dougherty Financial Group (DFG), DuVal and Associates (DVA), and the Minnesota Medical Device Alliance (MMDA) who have agreed to the inclusion of edited versions of their reports and commentary in *SurFACTS*.

Each report has a slightly different emphasis. DFG emphasize the effect

proposed changes might have on the investor community and consequent decreases in funding of start-up medical device companies. DVA comments specifically on the risk-averse nature of the FDA and the effects this cultural climate has on the industry. The MMDA position paper specifically voices the concerns of smaller medical device companies with any proposed increases in requirements for 510(k) clearance and makes its own recommendations for modifications. MMDA notes that smaller medical device companies, which are responsible for the introduction of the vast majority of innovative technologies to the marketplace, do not have the financial resources of larger device companies and will be affected to a greater extent by any increase in requirements than will larger corporations with greater financial resources.

Following are edited excerpts of their reports of the Minnesota Town Hall Meeting.

Report of the Dougherty Financial Group

The meeting was well attended by approximately 400 people, most of whom were clinical/regulatory experts, CEOs of private medical device companies, physicians, venture capital investors, et al. Approximately 25 percent of medical device industry revenues are tied to Minnesota, so we felt that it was appropriate for the FDA to have their first open door forum (outside of Washington D.C.) in Minneapolis.

- Dr. Jeff Shuren, current Director of CDRH gave a 20 minute overview of the 510(k) process and

timeline for changes. Dr. Shuren stated that FDA "has no intention to scrap the 510(k) process."

- Dr. Shuren emphasized that CDRH needs to be more transparent in what it does in the future so that it can improve the level of predictability for medical device companies.
- Dr. Shuren reiterated that FDA will not wait for the completion of the Institute of Medicine study to assess the 510(k) process due in March 2011 and that changes would be made in early 4Q 2010. These changes will be communicated to the industry after the end of May 2010.
- Dr. John Sherman, former Medical Director of the now defunct company Disc Dynamics stated his case contending that FDA's indecision participated in causing his company's demise.
- In his presentation, venture capital (VC) investor Peter McNerney of Thomas McNerney & Partners laid out a good case as to why VC investors have been pulling back from this sector. He and others stated that they believe the short job tenure of the average FDA reviewer and their lack of relevant experience have contributed to delays and other problems with the FDA approval/ clearance process.
- Dave Stassen of Splitrock Partners gave a compelling example of why the approval process was flawed and that the FDA was inconsistent in how it applies the statute. Dr. Shuren responded, "How we do things today is not acceptable."

Printed Origami Offers New Technique for Small, Complex Structures

By Liz Ahlberg, Physical Sciences, University of Illinois

Although it looks small and unassuming, the tiny origami crane sitting in a sample dish in University of Illinois professor Jennifer Lewis' lab heralds a new method for creating complex three-dimensional structures for bio-compatible devices, microscaffolding and other microsystems. The penny-sized titanium bird began as a printed sheet of titanium hydride ink.

The team published their novel technique on April 14, 2010, in the online edition of the journal *Advanced Materials*.

Small, intricate shapes made of metals, ceramics or polymers have a variety of applications, from bio-medical devices to electronics to rapid prototyping. One method of fabricating such structures is by direct-write assembly, which the Lewis group helped pioneer. In this approach, a large printer deposits inks containing metallic, ceramic or plastic particles to assemble a structure layer by layer. Then, the structure is annealed at a high temperature to evaporate the liquid in the ink and bond the particles, leaving a solid object.

However, as more layers are added, the lower layers tend to sag or collapse under their own weight – a problem postdoctoral researcher Bok Yeop Ahn encountered while trying to manufacture titanium scaffolds for tissue engineering. He decided to try a different approach: print a flat sheet, then roll it up into a spiral – or even fold it into an assortment of shapes. Folding the printed sheets is not as easy as it would first seem.

"Most of our inks are based on aqueous formulations, so they dry quickly. They become very stiff and can crack when folded," said Lewis, the Thurnauer Professor of Materials Science and Engineering and the director of the university's Frederick Seitz Materials Research Laboratory.

The challenge, then, was to find a solution that would render the printed sheets pliable enough to manipulate yet firm enough to retain their shape after folding and during annealing.

Lewis, Ahn and their research team solved the problem by mimicking wet-folding origami, in which paper is partially wetted to enhance its foldability. By using a mixture of fast-drying and slow-drying solvents in the ink, the sheet dries partway but stays flexible enough to fold through multiple steps – 15, in the case of the crane.

The U. of I. researchers worked with professor David Dunand, the James and Margie Krebs Professor of Materials Science at Northwestern University, who initially approached Lewis with the possibility of titanium hydride inks. "I knew how to transform hydride into metallic titanium without contamination from the ink, based on prior research in my lab," said Dunand, who focused on annealing the soft, titanium hydride origami structures into strong, metallic titanium objects.

The marriage of printing and origami techniques allows for greater structural complexity – such as the crane's overhanging wings, a feature not

producible by direct printing methods alone. In addition, Lewis' team can print sheets with a variety of patterns, adding yet another level of architectural detail.

"By combining these methods, you can rapidly assemble very complex structures that simply cannot be made by conventional fabrication methods," Lewis said.

Next, the team hopes to expand its origami repertoire to include much larger and much smaller structures, with an expanding array of inks. For example, the method can be extended to a variety of other ceramics and metals ranging from steels to nickel- and cobalt-based alloys to refractory and noble metals, according to Dunand.

The researchers also plan to explore possible applications including lightweight structures, biomedical devices, sensors and more.

"We've really just begun to unleash the power of this approach," Lewis said.

The Department of Energy-sponsored U. of I. team also included graduate student Christopher Hansen and visiting scientist Daisuke Shoji, of the Pentax-Hoya Corp., Tokyo. The NSF-sponsored Northwestern team included undergraduate student Eunji Hong (visiting from Kookmin University, Seoul).

Silk Implant Could Aid Spinal Injuries, Epilepsy

From Reuters

A brain implant made partly of silk can melt onto the surface of the brain, providing an “intimate” connection for recording signals, according to a recent study.

Tests of their device showed the thin, flexible electrodes recorded signals from a cat’s brain more accurately than thicker, stiff devices.

Such devices might help people with epilepsy, spinal cord injuries and even help operate artificial arms and legs, the researchers report in the journal *Nature Materials*.

John Rogers of the University of Illinois, Urbana and colleagues at the

University of Pennsylvania and Tufts University in Boston made the electrode arrays using protein from silk and thin metal electrodes.

The silk is biocompatible and water-soluble, dissolving into the brain and leaving the electrodes draped over its contours, the researchers reported. They tested them on cats who were anesthetized but whose eyes were functioning. The electrodes recorded the signals from the eyes of the cats as they were shown visual images.

“These implants have the potential to maximize the contact between electrodes and brain tissue, while minimizing damage to the brain,” said Dr. Wal-

ter Koroshetz of the National Institute of Neurological Disorders and Stroke, part of the National Institutes of Health, which helped pay for the study.

“They could provide a platform for a range of devices with applications in epilepsy, spinal cord injuries and other neurological disorders.”

For instance, such a sensitive electrode could detect a seizure as it starts and deliver pulses to counter it. Brain signals might be routed to prosthetics for people with spinal cord and other injuries.

Silk is also transparent, strong and flexible, and it is possible to control the rate at which it dissolves.

Biomaterial Stretches Like Muscle

By Corinna Wu, Technology Review

Many research groups are trying to develop materials with similar properties to muscles. One of the big difficulties is creating anything with just the right muscle-like elasticity – its ability to change shape while withstanding a large strain. Now researchers at the University of British Columbia (UBC) in Vancouver, Canada, have synthesized a protein-based material that stretches exactly like the real thing.

The new material achieves the elasticity of muscle by mimicking the microscopic structure of a giant muscle protein called titin. The structure of titin resembles a string with beads; globules of folded protein sequences are connected by floppy, unstructured sequences. Hongbin Li, a chemist at the UBC, and his colleagues constructed the new material that imitates this structure. They chose a mechanically stable pro-

tein sequence that folds in on itself to form globules and another protein called resilin to serve as the floppy connectors.

The result was a “mini-titin”—a protein that resembled titin structurally but is much smaller, Li says. The researchers chemically linked the individual protein strands together to form a hydrogel (a light, solid material that consists mostly of water) and then tested the material’s mechanical properties. The team describes the work in a recent issue of the journal *Nature*.

When they tested the material, Li and his colleagues found that it behaved much like real muscle tissue. When stretched a little bit, it bounces back like an elastic rubber band. If stretched more vigorously, the beadlike protein domains unfold, and it dissipates some energy before returning to its original state.

“It’s a nice progression along the lines of building an artificial muscle,” says physicist David Weitz of Harvard University, whose group studies the structure of muscle protein networks. Other groups are working on creating electroactive polymers, which contract when stimulated by an electric signal, so that the “muscle” can be controlled. The current material does not have this feature, but adding that would be “the next step,” Weitz says.

Artificial muscles could one day be used as scaffolds for growing muscle to repair damage in patients, in biologically compatible devices for medical applications, or even to control robots without using motors. However, since proteins tend to unravel at high temperatures and under harsh environmental conditions, this does not make them ideal for industrial applications.

Endoscopic Duodenal Stenting is Associated with Lower Costs and Shorter Hospital Stays Compared to Surgery for Relief of Malignant Gastric Outlet Obstruction

Boston Scientific Corporation announced results from a study demonstrating that endoscopic duodenal stenting is associated with lower costs and shorter hospital stays than surgical gastrojejunostomy (GJ) for the relief of malignant gastric outlet obstruction. Results of the study were presented at Digestive Disease Week® (DDW®) by Shyam Varadarajulu, M.D., Associate Professor of Medicine, Division of Gastroenterology & Hepatology, University of Alabama at Birmingham School of Medicine.

Endoscopic stenting is increasingly performed for the relief of malignant gastric outlet obstruction, a late complication of duodenal, pancreatic, gallbladder, biliary tract and small intestine cancers. An analysis of the Medicare database was conducted to identify hospitalizations for endoscopic stenting and surgical GJ for malignant gastric outlet obstruction between 2006 and 2008. The database included 423 endoscopic stenting and 352 surgical GJ hospitalizations that met the study inclusion criteria. Results showed that the median cost per hospitalization (\$15,279 vs. \$27,790, $p < 0.0001$) and the median length of hospital stay (LOS) (8 vs. 16 days, $p < 0.0001$) were significantly less for endoscopic stenting than surgical GJ. In addition, endoscopic stenting was more commonly performed at urban vs. rural, and teaching vs. non-teaching, hospitals.

The study also evaluated clinical outcomes for 29 patients who underwent endoscopic stenting and 75 patients who underwent surgical GJ at the University of Alabama at Birmingham Hospital, and compared rates of technical and treatment success, post-procedure LOS and delayed complications. While both treatment methods were technically successful and relieved malignant gastric outlet obstruction, the median post-procedure LOS was significantly shorter for endoscopic stenting than surgical GJ (1.5 vs. 10.7 days, $p < 0.0001$). There was no difference in rates of delayed complications.

"While the technical and clinical outcomes may be similar with the two methods of managing malignant gastric outlet obstruction, these results clearly demonstrate there are significant implications for patient care and resource utilization," said Dr. Varadarajulu. "In addition, it is important that endoscopic stenting extend beyond teaching hospitals located in urban areas."

Boston Scientific's WallFlex® Duodenal Stent was used in many of the stenting patients in the study. It is a large diameter, radiopaque, flexible, self-expanding metal stent designed to help maintain luminal patency in patients with gastroduodenal obstructions. The stent has looped ends and incorporates a flared design intended to reduce the risk of migration. The low profile, reconstrainable delivery system features a tapered tip to support access and


radiopaque markers to aid in placement accuracy.

"Palliation of symptoms is the primary treatment goal for patients suffering from malignant gastric outlet obstruction, and this study shows that stenting provides a less-invasive treatment option that is as effective as surgery but offers lower hospital costs and shorter hospital stays," said Michael Phalen, Senior Vice President and President of Boston Scientific's Endoscopy Division. "Boston Scientific is committed to endoscopic stent innovation that supports improved patient outcomes and reduced health care costs. The WallFlex Duodenal Stent reflects this commitment by providing advanced features that enhance stent deliverability, deployment and luminal patency."

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Composite Metal Foam Material Could be Tomorrow's Knee Cap

By Bob Michaels, Medical Product Manufacturing News

Scientists at North Carolina State University are developing a novel metal foam that they hope could serve as a replacement material for damaged bone in future orthopedic and dental implant applications. Because the material's modulus of elasticity are similar to that of bone, Professor Afsaneh Rabiei and former NC State PhD student Lakshmi Vendra believe that it can prevent bone rejection, which often occurs with more-rigid implant materials such as titanium.

Lighter than solid metals, composite metal foam (CMF) can be fabricated from a variety of different alloys, says Rabiei, an associate professor of mechanical and aerospace engineering and an associate member of the biomedical engineering faculty at NC State. CMF is made using prefabricated hollow spheres formed in a metallic matrix, both of which are made from the same material or two different materials. It is manufactured by casting molten metal around the hollow spheres or by mixing the spheres with metal powder and baking them in a furnace. The bone implant itself can be manufactured by casting or hot-pressing the CMF in a mold or by machining it to the desired shape.

"At first, we made steel-steel and aluminum-steel versions," Rabiei notes, "but now we are able to make our composite metal foams out of titanium, cobalt-chromium, and other metals or their combinations."

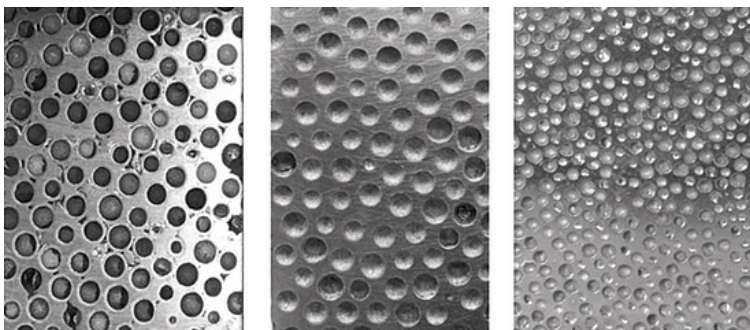
The composite foam is about 65% lighter than the bulk metal from which it is made, Rabiei remarks. "This means that it is about 65% porous. We can change the porosity percentage by controlling the diameter and wall thickness of the spheres. That way, we can match it with patients' bone porosity, considering their age or the condition of their bones."

Because it equalizes the load-bearing ability of the natural bone and the implant, the material is suitable for bone-replacement applications. "When an implant is placed in the bone, the two need to handle the load together," Rabiei explains. "If the bone's modulus of elasticity is lower than that of the implant, the implant will take over the bone's load-bearing function, causing the surrounding bone to die." This phenomenon, known as stress shielding, loosens the implant, resulting in eventual failure and the need for revision surgery. While bone's modu-

lus of elasticity—the measurement of a material's ability to deform under pressure and then return to its original shape when the pressure is removed—lies between 10 and 30 GPa, titanium's modulus is approximately 100 GPa. In contrast, CMF has a modulus that is consistent with bone. In addition, the porous, lightweight material exhibits high-energy absorption capability, and its rough surface fosters bone ingrowth.

A major goal of medical research is the development of implants with osseointegrative properties. The NC State scientists' metal foam material fulfills that function by allowing the bone to grow into the implant's porosities, enabling it to become anchored inside the bone. "Even if you use it together with a bone cement, the cement can form a nice interlock with the porosities of the foam," Rabiei says. "That secures the implant in the bone."

In addition to its potential benefits as a bone-replacement material, the CMF could be used in any application requiring a light, strong material, including medical devices for use inside or outside of the body.



Cut sections of aluminum-steel cast foam and 3.7- and 1.4-mm steel-steel powder metallurgy foam are examples of composite metal foams that could potentially be used in orthopedic implant applications.

- Dr. Shuren said that neither he nor Dr. Hamburg have changed the safety/efficacy directives for FDA reviewers.
- FDA 510(k) Approval Process- We expect the FDA to begin implementation of their changes to the 510(k) approval process by September 30, 2010 at the latest. There appears to be a sense that the current system which is based on predicate devices will be changed.
- The “closer” was Susan Alpert, Senior Vice President and Chief Regulatory Officer at Medtronic. Dr. Alpert, who spent six years at CDRH as the Director of the Office of Device Evaluation, gave a succinct presentation identifying “5 Asks” that she hoped would be addressed in the 510(k) redesign process. The five items she identified as essential for a successful redesign are that the new process be interactive; include clear messages; be predictable; be consistent; and allow time for the industry to prepare for and accommodate any new requirements.

DFG also provide a good review of the 510(k)-related events that have occurred and that are scheduled for the future.

Report and Comments of DuVal and Associates

It is clear that we have a strong leader at the helm at CDRH. Dr. Jeff Shuren displayed a firm grasp on the issues and challenges and has a clear idea how to solve them. He openly, calmly and candidly addressed questions

with warmth and well-placed humor. He is an effective leader and spokesman for the Agency.

- We think Dr. Shuren heard from the Minneapolis Town Hall crowd that there are real concerns with his organization from the standpoint of **predictability, transparency and reasonableness**.
- He seems to have a handle on issues concerning **predictability and transparency** and has ideas of how to resolve them within the Center. The problem may be that when CDRH uses the term “predictability” it may mean “predictably more” in terms of added processes (IDEs, submission reviews, handling dissent, appeals and advisory panels). If CDRH solutions end up streamlining these processes, then CDRH efforts will be a success.
- In the area of **predictability**, many of the speakers and people in the Q&A session raised the issue of the FDA’s/reviewer habits of implementing changes in guidance and expectations before guidance is published. Companies that follow FDA’s published guidance find that there are additional or new requirements only after submitting their applications when the FDA requests additional information.

DVA Comment: *FDA must resist the temptation to migrate to new thinking and impose it upon an applicant mid-stream until new guidance is actually formulated, aired out with the public and implemented. There is no need to change course precipitously unless there is a clear and present danger*

to the public. FDA’s propensity for requesting information beyond what is documented in its guidance documents is rooted in its risk averseness, discussed more below.

- We strongly believe Dr. Shuren when he says he wants the Agency to be more transparent. It already has been as evidenced by yesterday’s meeting.

DVA Comment: *We think this trend of increased transparency will continue, but bad news (more requirements, review and compliance oversight) delivered in the light of day is still bad news.*

DVA Comment: *Where we think there is still a disconnect between staff and management is in the area of **reasonableness**. After all, data requirements can be predictable and transparent but still be unreasonable. The Center is very risk averse and still seems to struggle with balancing the risk of letting go of a device with the benefit of getting it to patients sooner. CDRH needs to come to a deep-seated understanding that not everything is or can be within their control before a device is cleared or approved. Ever-es-calating data requirements are not the answer and will certainly kill innovation and investment in this sector. **This is the most vexing problem facing industry and will be the most difficult challenge for Dr. Shuren** who has to impact the review culture.*

DVA Comment: *In the pursuit of “safety,” the Agency must be careful not to exceed its statutory authority. The 510(k) statute only requires a sub-*

stantial equivalence determination and specifically precludes other considerations. The trend toward front-end loading 510(k)s with additional expectations reflects the Agency's aversion to risk.

DVA Comment: We believe that the Agency needs to re-familiarize, maybe resuscitate, Least Burdensome principles and bring them back to life.

DVA Comment: We know Dr. Shuren and his management are good listeners and they are dedicated and smart; we'll have to wait and see what they do with Minnesota's input.

Synopsis of the written comments addressed to Dr. Shuren and Colleagues by the Minnesota Medical Device Alliance

Re: Regulatory Perspective Presented at the Town Hall Meeting on May 18, 2010 in Minneapolis

- While we agree that appropriate testing is needed to support modified products and new technologies, we are very concerned that the standards are being raised unnecessarily high and that the requirements are continuing to change throughout the review process.
- Medical devices are generally made from well-known, well-characterized materials that have only a local effect on or within the human body. Therefore, medical devices need NOT be held to the types of data requirements to prove safety as those for pharmaceutical and biologic products.

- The laws passed by Congress recognize and account for the differences between medical devices and pharmaceutical products. There is a requirement for PROVING safety and effectiveness of a new, novel product via the Pre-Market Approval (PMA) pathway. This submission must be supported by extensive in vitro (bench), in vivo (animal) and human clinical testing. It is critical, however, that the testing requirements be appropriate and acknowledge the localized nature of the product application.
 - This point was emphasized in the Least Burdensome provision and highlighted a 510(k) pathway that takes the following into consideration: "FDA should eliminate unnecessary burdens that may delay the marketing of beneficial new products." This provision highlights that requested information only pertain to that which is necessary in making a substantial equivalence decision.
 - Current law also recognizes and accounts for a product type's history of successful device use in the marketplace. For products that represent only a small or incremental advancement, the history of safe and effective use, as evidenced by continued use by knowledgeable physicians, can be considered in the evaluation of safety and effectiveness. It is reasonable then to reserve the need for human clinical data only for

those situations in which the bench, animal testing, and clinical history is insufficient to address product differences.

- Furthermore, the law stipulates that "in making such requests [for information], the Secretary shall consider the least burdensome means of demonstrating substantial equivalence and request information accordingly."
- MMDA believes that the general framework from FDA's current 510(k) program is appropriate and can continue to be leveraged because the FD&C Act is sufficiently flexible to accommodate technological innovation, while allowing for FDA to request the data it needs to ensure safe and effective devices are coming to market.
- In support of the Agency's goal to ensure patient access to safe and effective medical devices while encouraging product innovation, we propose the following changes which can be made within the existing framework of the law and regulation:
 - Substantial Equivalence continues to be an important mechanism that affords the agency and industry to not have to "reinvent the wheel" in terms of substantiation of product performance. The existing body of experience provides valuable insight when viewed in conjunction with the existing body of clinical experience from similar products already on the market, affording the opportunity to

infer safety and effectiveness rather than having to prove it from baseline. The requirement to establish Special Controls offers further occasion to impart additional evidence of safety and effectiveness.

- Post-market options, including post-market surveillance and patient registries, are clearly cited as options for “special controls” which would provide reasonable assurance of the safety and effectiveness of the device.
- The De Novo approach, set forth in the FD&C Act, is a promising avenue for both FDA and industry when products do not neatly fall within the 510(k) pathway. The De Novo alternative presents a practical method for categorizing new low and moderate risk technologies as safe and effective with appropriate justification. The FDA, with industry’s input, needs to clearly define when and how De Novo can be used.
- Burdensome principles have fallen somewhat into disuse and are often absent at the forefront of FDA’s thinking. These principles need to be brought back into the FDA’s decision-making process.

MMDA’s written comments further detail proposed “practical solutions focused on mitigating risk [there will never be zero risk] and advancing technology that can be placed in the hands of clinicians to better serve their patients.” They specifically ad-

dress Predicate Devices, Indications and Intended device use, and “Device Creep” or the gradual shift in technology employed in devices serially cleared for the same intended use(s) by the FDA. Because of space limitations, these proposed solutions are not presented.

Summary

These three reports nicely summarize the Town Hall meeting, voice the concerns of the medical device community with changes to the 510(k) process that would increase the burden on manufacturers to bring their devices to the market, and propose modifications that could assure the safety and efficacy of new devices without unnecessarily increasing regulatory requirements.

Change always creates opportunities. The FDA now has an opportunity to modify the 510(k) process for the better. However, the need for modification is not urgent. There is not a mandate to change the 510(k) process because it is inherently broken or because devices cleared by this process that are currently on the market are unsafe. So if indeed the 510(k) process needs to be changed, then here is my short list of modifications to the FDA’s mechanism for clearing low and medium risk (currently identified as Class I and Class II devices by the FDA) medical devices:

- Further harmonize the FDA pre-market notification process with the approval processes of other countries and geographic areas. The requirements for demonstrating that devices are safe

and effective and the benefits of their use outweigh inherent risks should be the same regardless of where a device is used.

- Require clinical data to establish the clinical safety and performance of all medical devices. I mean “Clinical data” as it is defined in the European System (See MEDDEV 2.7.1 – Evaluation of Clinical Data: A Guide for Manufacturers and Notified Bodies and GHTF SG5/N2R8:2007- Clinical Evaluation). The requirement for “substantial equivalence” comes into play as it is required in order to enable a submission sponsor to leverage information in the published clinical and other literature for the device type under scrutiny. If the new device has features or uses whose SE has not been previously established clinically and cannot be demonstrated using pre-clinical and bench data, then a clinical investigation (trial) would typically be required. The confidence required of the results (sample size) would be proportional to the risks posed by the new features and uses.
- The safety and performance requirements for a device should be risk-based, and the risk assessment should be the central document in determining the ability to legally market the device. All risks need to be mitigated or controlled, and the means of control need to be verified with bench data and the results of simulated use studies. This approach is currently followed by the FDA for “special premarket notifications.” It should be extended to address all devices.

- I agree with others that the “De Novo” process is appropriate for the categorization of devices that are not legally defined under the current system.
- The use of standards and “special controls” should be expanded and utilized to a greater extent.
- The FDA has to have authority to remove devices from the market that it can demonstrate to be unsafe or that the manufacturer cannot demonstrate to be state-of-the-art. When the FDA has refused to recognize the use of predicate devices in new 510(k) submissions it is, de facto, stating that these devices are no longer acceptable. If these devices cannot be used as predicate devices, then they shouldn’t be on the market.

I realize that these changes would require modifications to the current code, and this would take time, but there is no urgent need for change. I fear that attempts to quickly “fix” a system that isn’t broken may not be in the best interests of the FDA, patients, clinicians, or medical device manufacturers, especially if they enforce a tendency to add regulations in the hopes of enhancing the safety of devices placed on the market. Public perception of the Agency may improve, but not the availability or quality of medical devices or health care available to the American public.

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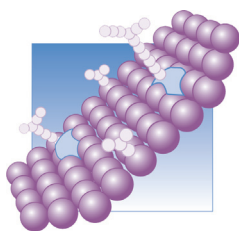
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