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Fall 2014
Volume 19, Issue 4

From the Editor

BioInterface 2014 was held in Redwood City, California from October 6th through 8th and once again was another great meeting. This first day consisted of an excellent workshop describing the many different roles that must be played to take a device from idea to product. While it is a given that being a successful medical technology entrepreneur requires an innovative technology, this workshop highlighted the additional skill-sets and expertise required to bring a product to market. This includes considerations of marketing, fund raising, intellectual property, regulatory approvals, product development and distribution into different geographical territories. Understanding all these items is important regardless if you are at a start-up or a large, established firm. The first day concluded with applied technology workshops and a keynote speech by Kevin Healy from U.C. Berkeley.

Day two covered surface characterization, new developments in device coatings, and ophthalmology, and concluded with a point-counterpoint on the impact of FDA on innovation with anti-infective technologies. The debate was won by David Granger arguing against a positive role for the FDA, but many good points were also raised by his competitor Clark Thompson who challenged the industry that they needed to generate good data justifying their technologies.

Day three featured sessions on hemocompatibility, cell response at the nano-interface, anti-infective technologies, and developments in trans-catheter heart valves. It also included a lively, presentation by the SIBF Award Winner, Thomas Fogarty. Dr. Fogarty warned against the obstacles impeding innovation in the United States, but also offered an inspiring take on the qualities required to be a successful innovator.

I enjoyed the chance to meet with everyone at the meeting and am looking forward to being in Arizona in 2015. Many thanks to our sponsors: DSM Biomedical, Evans Analytical Group and Edwards Life Sciences. We are already working on programming for next year which will be the 25th anniversary of BioInterface. If you have any programming ideas or have an

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INSIDE THIS ISSUE

Members are encouraged to submit articles for future editions of SurFACTS. Please e-mail your report (with all appropriate figures and graphics) to Staff Editor Jazzy McCroskey at jasperm@ewald.com for consideration in a future issue. Deadlines for upcoming issues are posted on surfaces.org.

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interest in chairing a session please contact SIBF, myself or Rob Kellar who will be in charge of planning the meeting.

SIBF Open House at NAMSA

The Annual SIBF open house was held on September 11th at NAMSA in Minneapolis. The open house featured presentations from NAMSA employees on NAMSA's Medical Research Organization approach, risk assessments and biostatistics. The event concluded with a tour of the NAMSA preclinical lab in Brooklyn Park, Minnesota.

SAVE THE DATE

BioInterface 2015
September 21-23, 2015

FAIRMONT SCOTTSDALE
Princess

Scottsdale, Arizona – U.S.A.

Member News

CSIRO in partnership with St. Vincent's Hospital and Anatomics carried out the world's first surgery to implant a 3D printed titanium bone implant. They also announced the selection of Dr. Larry Marshall as their new Chief Executive replacing Dr. Megan Clark.

Boston Scientific obtained CE mark approval for a number of products including CoverEdge™ X 32 Surgical Leads, an MRI compatible pacemaker, the Vercise™ Deep Brain Stimulation System, and the Agent™ drug-coated balloon. The COVEREDGE surgical leads which also received FDA approval have double the number of independent contacts to provide more focused coverage and pain relief. The company also received a favorable FDA panel vote for its WATCHMAN™ left atrial appendage closure device for treatment of stroke in patients not-amenable to anti-coagulation. Boston Scientific also began enrolling US patients in a clinical trial of its second generation Lotus™ transcatheter valve system.

Corline Systems received EU orphan drug designation for the CHC™ compound for prevention of ischemia/reperfusion injury associated with kidney transplantation. CHC is a heparin compound applied to the kidney ex vivo prior to transplantation that self organizes on the blood vessel of the organ to protect against inflammation and thrombosis when the organ is reconnected to the patient blood supply.

Medtronic received FDA approval of its CapSureFix Novus™ MRI-compatible pacing lead system and began a pivotal trial of the innovative, predictive, low glucose management technology which uses a pump and continuous glucose monitoring. The company also received CE Mark and launched its TYRX™ absorbable antibacterial envelope in Europe. In the spinal area, Medtronic launched the new Divergence™ cervical fusion system and new products in the KYPHON™ balloon kyphoplasty technology for treatment of fractures. The KYPHON system gives added control of delivery of bone cement to fractures. Medtronic also acquired NGC Medical, a manager of operating suits and ICUs, and Sapiens Steering Brain Stimulation, a maker of deep brain stimulation technologies.

Keith Edwards, President and CEO of **Biocoat** will be speaking at MD&M Minneapolis on medical coatings. A preview of his talk can be found on Qmed titled "What You Need to Know about Medtech Coatings". The company also released a video on pinch testing experiments available for viewing on its website.

W.L. Gore received FDA approval for endovascular treatment of in-stent restenosis using the GORE® VIABAHN® Endoprosthesis. This approval changes the treatment paradigm for restenosis by re-lining the failed bare metal stent to provide prolonged vessel patency more effectively than angioplasty

Covidien began in enrollment in two neurovascular clinical trials. The first trial named PREMIER will

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Member News continued from pg. 3

investigate the use of the Pipeline™ flow diverter device in small unruptured intracranial aneurysms. The second trial is the STRATIS Registry which will evaluate use of all market-released Covidien stroke devices. The company also announced the acquisition of Sapheon, Inc., makers of the VenaSeal® system for closing veins and Reverse Medical, maker of vascular embolization plugs for vessel occlusion.

DSM Biomedical announced that its Bionate®II PCU and BioSpan® SPU will be used in the ReligaHeart EXT ventricular assist device. This device will take advantage of the flex life, biocompatibility and stability of these materials. They also released a new material, Somos® Precise, for 3D printing of dental aligners as well as a new radiopaque version of their Dyneema Purity® UHMWPE fiber. DSM also launched a cellular therapy development business to assist in all the paths of cell therapy from isolation and concentration through delivery independently or with biomaterials. The first product offering is a concentrator for rapid preparation of platelet rich plasma.

Ex Thera Medical announced the conversion of a $3.75 million convertible note to fund completion of the first clinical trial with the Seraph® Microbind® Affinity Blood Filter. The company also appointed John Feik, a pharmaceutical industry veteran, to their board of directors.

CooperVision announced the acquisition of Sauflon Pharmaceuticals a European maker and distributor of contact lens products in a transaction valued at approximately $1.2 billion. The acquisition should increase the number of product offerings for distinct wearer segments worldwide.

Bausch and Lomb announced an agreement between its parent company Valeant and Croma pharmaceuticals that will allow distribution both in Western Europe and the US. This will expand Bausch and Lomb's product portfolio by hundreds of distinct medical products. The company also announced Expanded Power Range availability for the TRULIGN™ Toric intraocular lens.

American Preclinical Services made several moves to expand their pathology capabilities. Dr. Lynette Phillips and Dr. Adrienne Shucker both joined the company in fall of 2014 as staff pathologists. They also added a second EXAKT ground sectioning machine to their equipment inventory.

St. Jude Medical received CE Mark Approval for MRI compatible pacing leads and launched the OPTIS integrated system of OCT imaging to be used in combination with angiography. The company also released new data from their CHAMPION clinical trial looking at the CardioMEMS™ HF System in patients

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.

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TOF-SIMS ANALYSIS OF BIOMATERIALS: SURFACE ANALYSIS, IMAGING, AND COMPOSITIONAL DEPTH PROFILING OF CONTACT LENS MATERIALS

By Paula A. Clark[1], Birgit Hagenhoff[1,2], Reinhard Kersting[2], and Elke Tallarek[1,2]
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INTRODUCTION:

Many important properties like adhesion, friction, oxidation, wettability, and biocompatibility are determined by a material's chemical composition. Moreover, these properties are governed by compositional differences that extend to difference depths. For example, wettability, which influences bonding and adhesion, is determined by the composition of the outermost atomic layers. In contrast, the appearance and the color of a material might be influenced by compositional differences that extend to a depth of 100 nm. In order to build appropriate structure – property relationships, there is an increasing need for analytical techniques which facilitate the identification, the localization, and the quantification of substances on the surface and at the interfaces between layers. This article will highlight the application of Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS) for the analysis of contact lens materials.

PRINCIPLE OF SECONDARY ION MASS SPECTROMETRY:

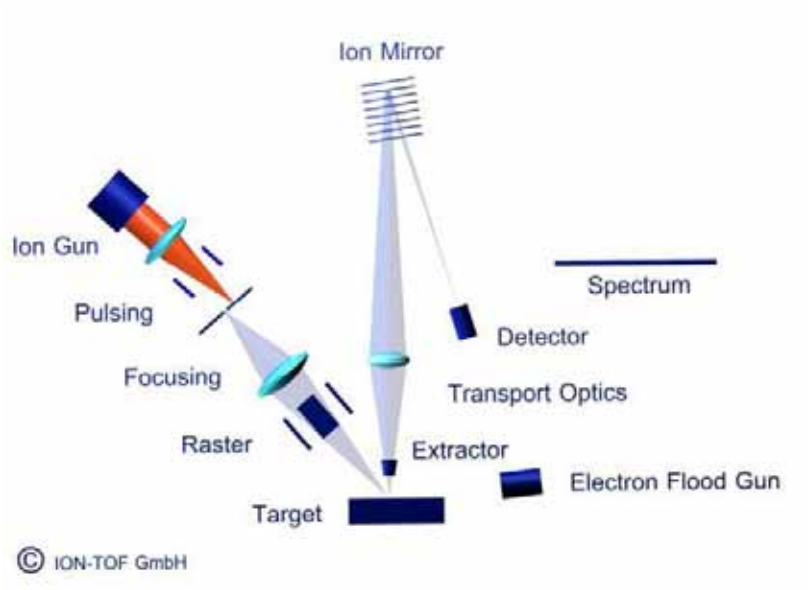

Figure 1. A schematic of a ToF-SIMS instrument. A pulsed primary ion source is used to desorb (sputter) secondary ions from the surface of the sample. The secondary ions are mass analyzed in a time-of-flight mass spectrometer. Courtesy of ION-TOF GmbH

Figure 1 shows a schematic of a ToF-SIMS instrument. In SIMS, a sample is introduced into an ultra-high vacuum chamber and bombarded with a pulsed primary ion beam. The impact of the primary ion results in the desorption (sputtering) of neutral species, electrons, and secondary ions from the surface of the sample. The secondary ions are mass analyzed in a time-of-flight mass spectrometer. The advantages of SIMS include high sensitivity to both elemental and molecular species, isotopic sensitivity, and imaging.[2] Simultaneous detection of secondary ions along with the ability to obtain this information with high lateral and in-depth resolution makes ToF-SIMS well suited for the analysis of structured materials.

The three operational modes available in ToF-SIMS include: surface spectrometry, imaging, and depth profiling. Surface spectrometry provides information on the composition of the uppermost 1 – 3 monolayers with sensitivities at the ppm level. In most cases, the spectra are recorded with high mass resolution where limiting the number of primary ions guarantees the secondary ion mass spectrum is representative of the chemical composition of the sample surface (i.e., static SIMS limit). Although SIMS is not inherently quantitative, relative comparisons of chemically similar samples are possible using a suitable normalization. ToF-SIMS imaging employs a focused primary ion beam to probe the surface of interest and a complete spectrum is recorded at each pixel. The lateral resolution is 3 – 5 µm for high mass resolution and 100 – 300 nm at nominal mass resolution. ToF-SIMS depth profiling is used to investigate the chemical composition of a solid as a function of depth.

TOF-SIMS ANALYSIS OF BIOMATERIALS: SURFACE ANALYSIS, IMAGING, AND COMPOSITIOAL DEPTH PROFILING OF CONTACT LENS MATERIALS continues on pg. 5

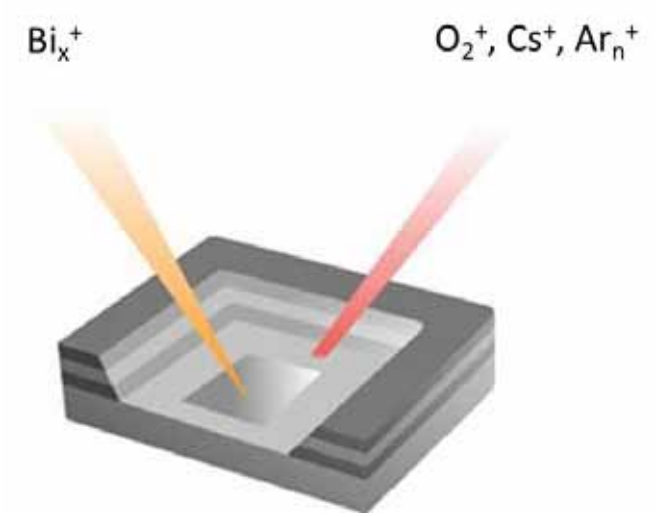

Figure 2. The ToF-SIMS dual-beam depth profiling experiment uses two ion beams: A sputter beam (e.g. O_2+, Cs+, Ar_n+) is optimized to create a crater in the sample and an analysis beam (e.g. Bi_x+) is optimized to analyze the crater bottom.

Figure 2 illustrates the principle of dual-beam depth profiling. In a dual-beam depth profiling experiment, the data are acquired using two separate ion beams: A sputter beam (e.g. O2+, Cs+, Arn+) is optimized to create a crater in the sample and an analysis beam (e.g. Bi_x+) is optimized to analyze the respective crater. The ToF-SIMS data file stores the lateral and in-depth position of all detected secondary ion signals; therefore, it is possible to reconstruct secondary ion images as a function of the X, Y, and Z cube coordinates. The ability to reconstruct images at XZ and YZ-cuts is particularly useful for locating species at buried interfaces.

APPLICATIONS:

Surface Spectrometry of Commercial Contact Lens Materials

ToF-SIMS was used to investigate the surface composition of two commercial contact lens materials. Lens material I is composed of 2-hydroxy-ethyl methacrylate (HEMA) and glycerol methacrylate.[3] This lens material composition was developed to mitigate discomfort due to “dryness.” Lens material II is composed of 2-hydroxy-ethyl methacrylate (HEMA) and 2-methacryloxyethyl phosphorylcholine cross-linked with ethyleneglycol dimethacrylate.[3] The addition of the phosphorylcholine improves biocompatibility by mimicking the polar lipids found in cell membranes; this helps maintain hydration and decrease protein deposition.

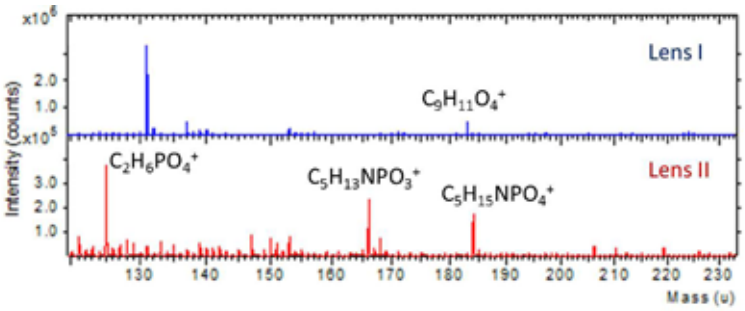

Figure 3. Positive secondary ion ToF-SIMS spectra acquired from Lens I (top) and Lens II (bottom). Lens I is characterized by O-containing hydrocarbons CH_3O+, C_2H_5O+, C_3H_7O+, and $C_9H_{11}O_4$+. Lens II is characterization is characterized by O-containing hydrocarbons and additional peaks from the phosphorylcholine component $C_2H_6PO_4$+, $C_5H_{13}NPO_3$+, and $C_5H_{15}NPO_4$+.

Figure 3 shows the positive secondary ion ToF-SIMS spectra acquired from Lens I (top spectrum) and Lens II (bottom spectrum). Lens I is characterized by a series of O-containing hydrocarbons including CH_3O+, C_2H_5O+, C_3H_7O+, and $C_9H_{11}O_4$+. These peaks are characteristic of the HEMA material. Lens II is characterization is characterized by these O-containing hydrocarbons and additional peaks from the 2-methacryloxyethyl phosphorylcholine component: $C_2H_6PO_4$+, $C_5H_{13}NPO_3$+, and $C_5H_{15}NPO_4$+. The data demonstrate the sensitivity of ToF-SIMS to detect differences in the molecular composition of contact lens materials.

Imaging and Depth Profiling of Used Contact Lens

ToF-SIMS was also used to characterize a HEMA based contact lens which had been worn for about 2 weeks. A coating of proteinolipidic film will form on the surface of a contact lens immediately upon insertion into the eye[4]. The proteinolipidic film typically consists of lysozyme and lipids such as fatty acids and cholesterol.[5]

TOF-SIMS ANALYSIS OF BIOMATERIALS: SURFACE ANALYSIS, IMAGING, AND COMPOSITIOAL DEPTH PROFILING OF CONTACT LENS MATERIALS continues on pg. 6

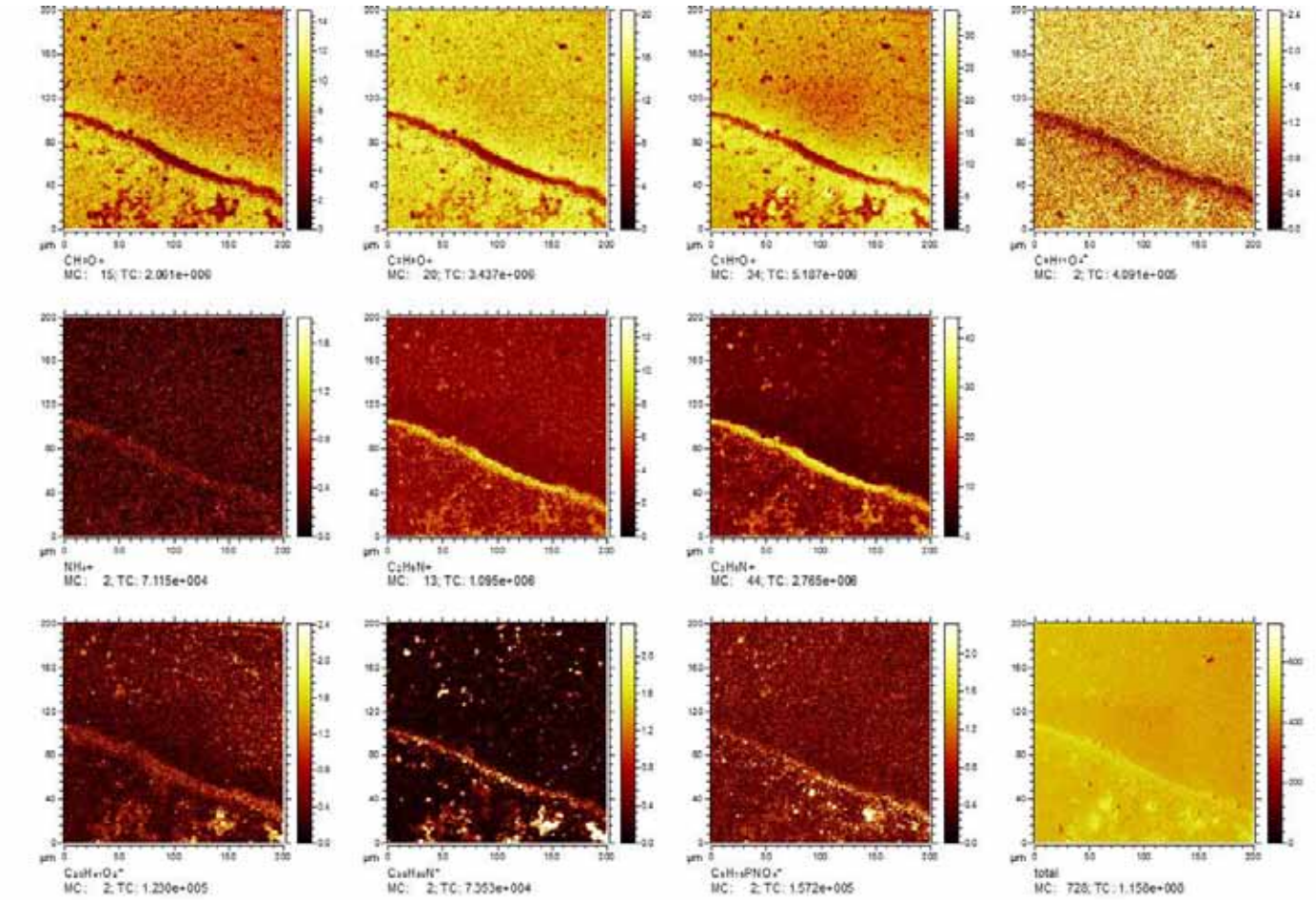

Figure 4. ToF-SIMS images acquired from a used HEMA-based contact lens. The images show the distribution of O-containing hydrocarbons characteristic of HEMA, the low-mass N-containing hydrocarbons, the fatty acid ($C_{20}H_{41}O_2$+), the diallyldimethyl ammonium ($C_38H_{80}N$+), and the phosphorylcholine ($C_5H_{15}NPO_4$+) on the surface of the contact lens.

Figure 4 shows the ToF-SIMS images acquired from the used contact lens. The analysis reveals the presence of a series of oxygen-containing hydrocarbons from HEMA (e.g. CH_3O+, C_2H_5O+, C_3H_7O+, and $C_9H_{11}O_4$+), low-mass N-containing species (e.g., NH_4+, C_2H_6N+, and C_3H_8N+) which may be indicative of amino acids (protein fragments), fatty acids ($C_{20}H_{41}O_2$+), possible phosphorylcholine ($C_5H_{15}NPO_4$+), and diallyldimethyl ammonium ($C_{38}H_{80}N$+). The diallyldimethyl ammonium chloride is thought to originate from the disinfecting solution used by the contact lens wearer.

The used contact lens was further analyzed using Ar gas cluster ion beam (Ar GCIB) depth profiling. An exciting advancement in the last 5 – 10 years has been the development of cluster primary ion sources (e.g., Au_n+, Bi_n+, SF_5+, C_{60}+, and Ar_n+). Relative to atomic primary ion sources, cluster sources provide higher secondary ion yields and therefore higher sensitivity. Moreover, C_{60}+ and Ar_n+ primary sources appear to directly remove the ion-beam-damaged area thus facilitating molecular depth profiling; i.e., the ability to monitor molecular species as a function of depth into the sample.[6,7,8]

TOF-SIMS ANALYSIS OF BIOMATERIALS: SURFACE ANALYSIS, IMAGING, AND COMPOSITIOAL DEPTH PROFILING OF CONTACT LENS MATERIALS continues on pg. 7

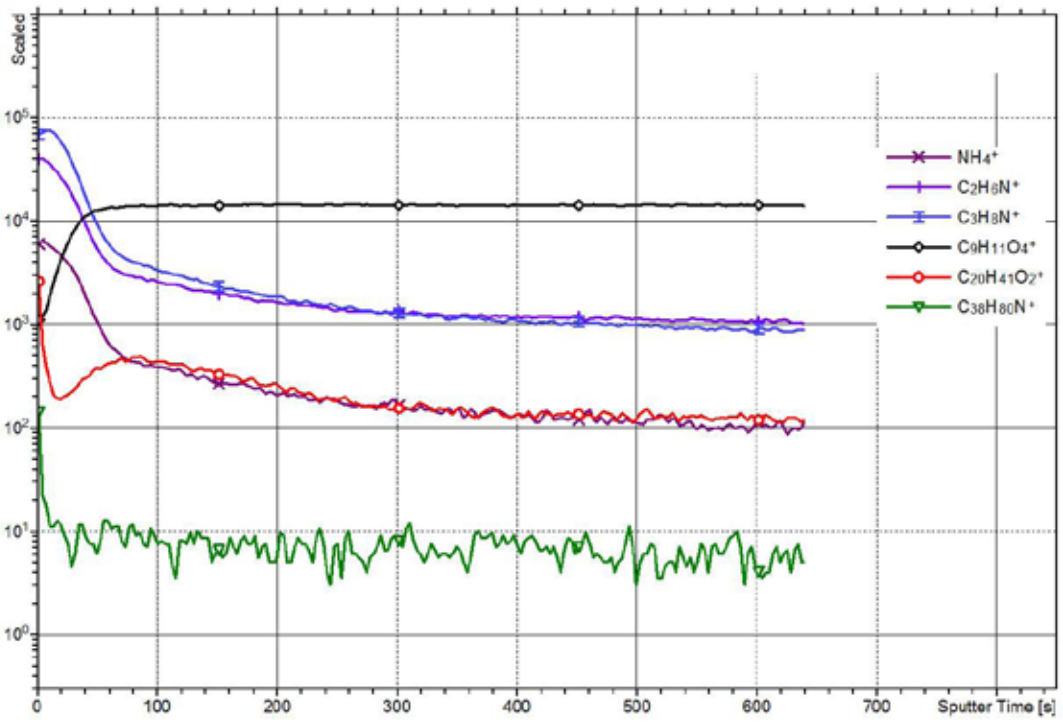

Figure 5. Ar GCIB depth profile of used contact lens shows the intensity of secondary ion signals as a function of sputter time. The N-containing species, the fatty acid, and the diallyldimethyl ammonium species appear to be concentrated at the surface region. Insert of C_3H_8N+ imaging shows low-mass N-containing species are deposits.

Figure 5 shows the Ar GCIB depth profile acquired from the used contact lens. In general, the intensity of the N-containing species, the fatty acid, and the diallyldimethyl ammonium species decrease with sputter time and thus appear to be concentrated at the surface region. The intensity of the O-containing species associated with the HEMA-based contact lens (e.g., $C_9H_{11}O_4$+) increase with sputter time.

SUMMARY:

In closing, ToF-SIMS has emerged as an important analytical tool for the characterization of a wide range of materials. The advantages of SIMS include high sensitivity to both elemental and molecular species, isotopic sensitivity, and imaging. Moreover, the development of Ar_n+ gas cluster ion sources for molecular depth profiling is a major advancement in the characterization of organic and polymeric materials.

In this application, the data demonstrate the sensitivity of ToF-SIMS to identify differences in the molecular composition of two commercial contact lenses. Imaging and depth profiling analysis further reveal the lateral and in-depth distribution of contaminants present on the used contact lens.

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Using Nanotopography and Nanoparticles to Fight Bacterial Infections

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Background on Healthcare-associated Infections

Bacterial infections are illnesses caused by bacterial pathogens including *Streptococcus, Staphylococcus, Pseudomonas, and E. coli*. They can result in mild infections that may be treatable using antibiotics. Bacterial infections can also lead to serious and deadly diseases such as bubonic plague, tuberculosis, and cholera. In hospitals and other health care facilities in the U.S. and Europe alone, more than 5.8 million patients each year develop life-threatening illnesses such as severe pneumonia, urinary tract infection and bloodstream infections from bacterial pathogens, while receiving treatment for medical or surgical ailments [1]. These patient-related bacterial infections, that originate from healthcare settings and are acquired from the surfaces of contaminated biomedical and non-biomedical devices, are called healthcare-associated infections (HAIs). Globally, hundreds of millions of patients are affected by HAI every year [1]. HAI represents a significant global problem and one, which must be managed urgently.

In addition, HAIs are associated with a high health cost to patients, and may result in morbidity and mortality. The most recent reports on HAI by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) estimate that in the U.S., 1.7 million HAI cases are reported annually with expenditures of approximately US$ 6.5 billion to treat these patients [2, 3]. Similarly, approximately 4.1 million cases of HAI are reported each year in Europe with an estimated 37,000 associated deaths and € 7 billion (US$ 9.2 billion) in associated medical costs [1]. Sources of HAI vary but often include medical devices, environmental contamination, surgical procedures, and contaminated injections, transfusions and wound dressings [3]. For example, device associated infections (i.e., central intravenous catheters infections, endotracheal catheters infections, and urinary catheters infections) have been reported to account for 25.6% of HAIs [2]. Prosthetic device infections from new implants (such as total hip and knee arthroplasties, pacemakers and mechanical heart valves) are also very common causes of HAIs in hospitals, often requiring corrective surgery to remove the contaminated device and stop the infection [4, 5].

Available treatments for HAI are increasingly limited because bacterial pathogens develop resistance against antibiotics. Approximately 70% of HAIs in the U.S. are resistant to one or more antibiotics because of the prevalent use of these drugs [6]. Traditional antibiotics are therefore ineffective for the majority of these patients. A growing and promising alternative approach in preventing bacterial function that results in infections is to modify the surfaces of medical devices, biomaterials and common material surfaces to possess nanotopographies (nanometer-sized structured surfaces) or by using nanoparticles (materials with at least one dimension at scales of 1-100 nm) [4, 7-10].

Why Nanotopography and Nanoparticles?

Conventional antibiotics kill and stop the growth of bacteria by chemically hindering their biological functions (i.e., cell wall synthesis, DNA replication, RNA transcription and protein synthesis) [6]. This approach of managing bacterial infections, although historically very effective, has become unsuccessful in recent years because bacterial pathogens develop genetic tolerance to these drugs within a few years of their commercial use [6, 11]. In the case of device-related infections, bacteria will attach and form a sticky antibiotic-resistant-biofilm matrix on the surface of these materials, prevent proper function of the device, and will require long-term treatment or removal of the device to heal the infection [4].

The use of nanostructured features or nanoparticles on biomedical devices is a rapidly growing approach to fight or prevent the occurrence of antibiotic-resistant bacteria and biofilms that may result in HAIs. Various nanotopographies or nanoparticles, in the

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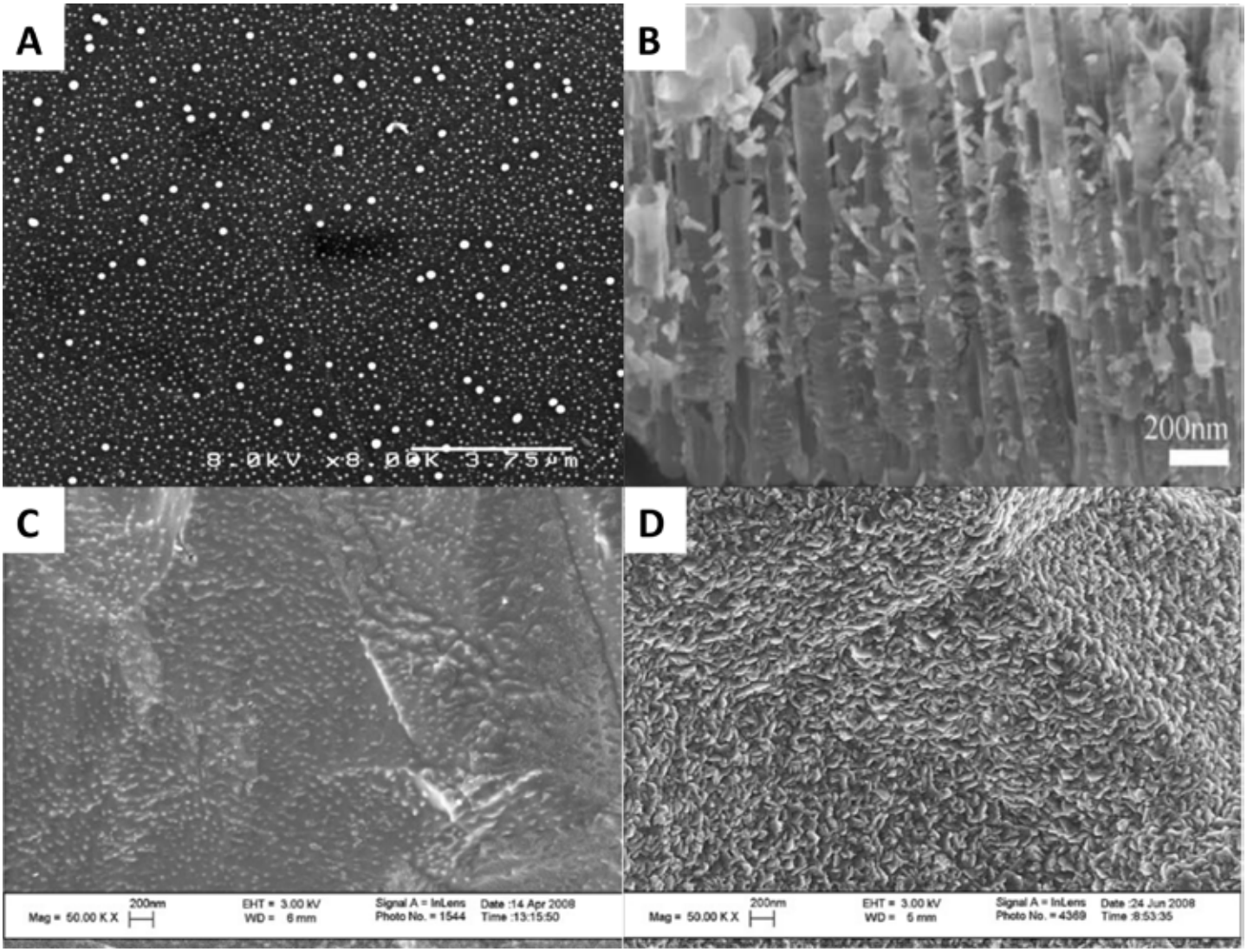

Figure 1. Various nanoparticles and nanotopographies used for anti-bacterial biomedical applications. Scanning electron micrograph (SEM) image of a selenium-nanoparticles-coated polycarbonate sample (A) [13]. SEM of TiO2 nanotubes loaded with 0.075 M ZnO nanoparticles (B). SEM images of conventional microtopography titanium (C) and nanotopography titanium (D) [19]. Note: (A) is reproduced from Wang et al. [13], (B) is reproduced from Liu et al. [7], (C-D) are reproduced from Puckett et al. [19], with permission from the publishers.

form of particles or tubes, have been developed and evaluated for their anti-bacterial properties in biomedical devices. Nanoparticles including selenium [12, 13], hydroxyapatite [14], ZnO [15], and TiO2 nanotubes loaded with ZnO nanoparticles [7] have been studied alone, and as components in fibrous materials, in composites, and on the surfaces of devices. Figure 1A-B shows respective images of selenium nanoparticles [13], and TiO2 nanotubes loaded with ZnO nanoparticles [7]. Nanoparticles attach to bacterial cell walls, damage the membrane of the cells by direct interactions or by free radical production [16], decrease the expression of bacterial adhesion genes [7], and inhibit the growth of bacteria [7, 9, 10, 14].

Novel nanostructure material surfaces including silicon nitride [17], zinc oxide [18], TiO2 [18], titanium [19], and poly(lactic-co-glycolic acid) [20] have been studied for their antibacterial properties. Representative images of conventional microtopography titanium and nanotopography titanium are illustrated in Figure 1C-D, respectively [19]. Innovative biomaterials engineered to have a combination of distinct nano-sized surface roughness, surface energy, surface chemistry and crystallinity, inhibit bacterial growth and biofilm formation for potential biomedical applications [17-20]. In addition, as topographical features of biomaterials are reduced from micron-sized to nano-sized, antibacterial properties are enhanced in part due to the increased surface charge,

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as well as enlarged surface area to volume ratio exhibited by the nano-structured biomaterials [21].

Introducing Nanotopography and Nanoparticles to Reduce Bacterial Functions

Titanium is one of the widely used metal for orthopedic implants [14]. The surfaces of titanium prosthesis devices such as total hip and knee arthroplasties are also prone to antibacterial-resistant bacterial and biofilm growth, which may greatly reduce the efficacy of these implants [4, 7, 14]. Zinc oxide nanoparticles possess anti-bacterial and osteogenic properties [7]. Anti-bacterial studies conducted by incorporating even distribution of ZnO nanoparticles on TiO2 nanotubes showed that the combination of these nanoparticles inhibited the growth of *Streptococcus mutants* (*S. mutans*) and *Porphyromonas gingivalis* (*P. gingivalis*) by 45-80%, compared to bare titanium nanotubes (Figure 2) [7].

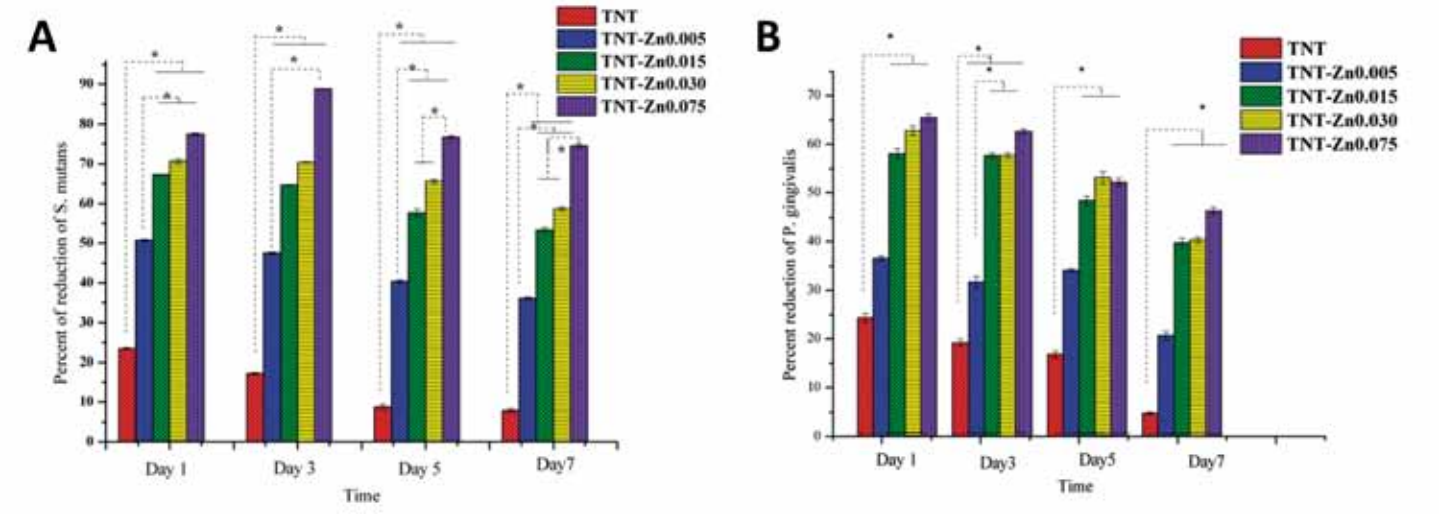

Figure 2. Reduction rates of S. mutans (A) and P. gingivalis (B) on titanium nanotubes (TNT), TNT with ZnO of composition 0.005M, 0.015M, 0.03M and 0.075M [7]. Figure on the right shows the fluorochrome micrography of stem cells cultured on (a) Ti, (b) TNT, (c) TNT-ZnO 0.005, (d) TNT-ZnO 0.015, (e) TNT-ZnO 0.030 and (f) TNT-ZnO 0.075. Note: (A-B) is reprinted from Liu et al. [7] with permission from the publisher.

Figure 2 illustrates the percent of reduction of S. mutans and P.gingivalis on the bare titanium nantubes and titanium nanotubes with 0.005M, 0.015 M, 0.030M and 0.075M of ZnO nanoparticles [7]. This study also reported that there is uninhibited growth of mesenchymal stem cells, cell that are able to differentiate into multiple cells types, on titanium nanotube coated with ZnO nanoparticles (0.015 M ZnO) [7]. The results presented here indicate that the equivalent samples which greatly reduced bacterial growth (0.015 M precursor Zn(NO3)2 samples) did not hinder mesenchymal stem cell growth.

For example, following culture of the bacteria line *Staphylococcus aureus* (*S. aureus*) on conventional microtopography titanium (Figure 3A) and nanotopography titanium (Figure 3B), a significant reduction in bacteria cell attachment was observed on the nano-sized surface compared to the micro-sized surface [19]. This study found that surfaces featuring nano-sized structures might be useful for reducing bacteria adhesion compared to micro-sized structures.

Summary

In conclusion, modifying the surfaces of biomedical devices to possess nanotopographies or by using nanoparticles may reduce the growth of antibiotic-resistant bacteria and biofilms that result in HAIs. TiO2 nanotubes loaded with ZnO nanoparticles, and titanium with nano-sized surface features were shown to reduce bacterial growth. The use of nano-structured features or nanoparticles on biomedical devices represents a promising alternative approach to managing HAIs.

Using Nanotopography and Nanoparticles to Fight Bacterial Infectionss continues on pg. 11

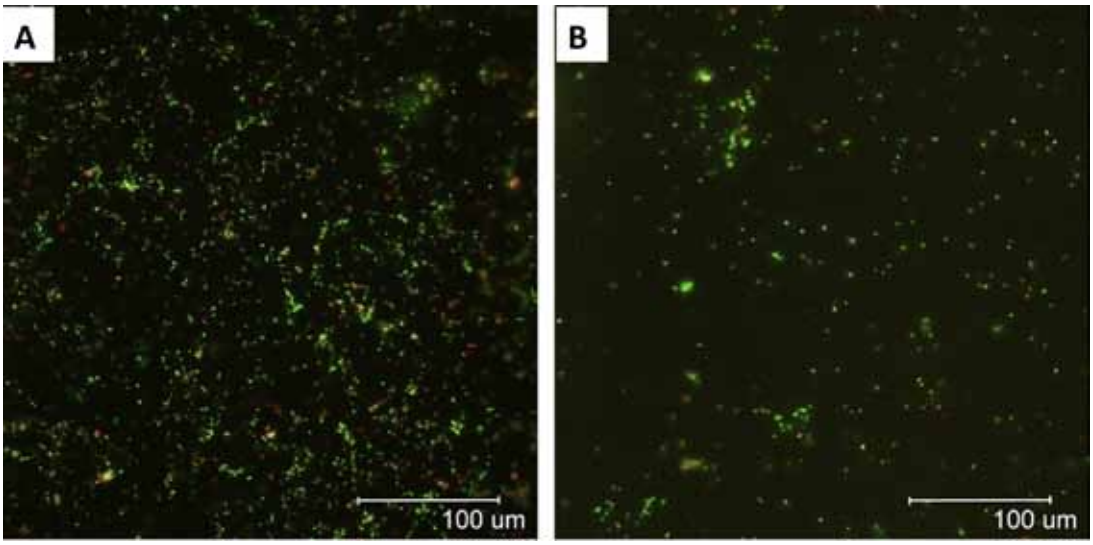

Figure 3. Fluorescent micrographs of diminished growth of S. aureus colonies on conventional microtopography titanium (A) compared to nanotopography titanium (B) after 1 h [19]. Bacteria cells were stained with the BacLight Live (green) / Dead (red) solution. Note: (A-B) is reprinted from Puckett et al. [19] with permission from the publisher.

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Unique and Common Aspects of FDA Clearance and CE Marking of Medium Risk Devices

By Phil Triolo

Because CE Marking of your device allows, at least theoretically, access to the entire EU as well as other markets, there is a great interest in evaluating a new device and creating documentation to meet the device premarket requirements of both the FDA and the EU (as provided in the Medical Devices Directive, MDD 93/42/EC). This article identifies the additional documentation and data needed to meet MDD requirements if a 510(k) was planned, and to meet 510(k) requirements if CE Marking was contemplated. The article assumes that the device to be marketed will be classified into Class II in the US, and IIa or IIb in the EU.

Note that once testing is initiated to meet regulations in one country, it often needs to be repeated to meet regulations in other jurisdictions. However, planning in advance can allow all test requirements to be addressed concurrently or simultaneously, reducing overall costs and development time.

Assuming that you are planning to submit a 510(k) to market your new device in the US, in order to also address CE Mark requirements you must plan ahead. The Design and Development Plan created at the beginning of the development cycle has to include the following tasks in addition to those already identified to meet FDA Design Control requirements:

- Implementation of standard operating procedures to meet EN ISO 13485 Section 7.1 and 7.3 requirements for Planning of Product Realization and Design and Development, respectively. These would supplement the Design Control procedures that must be implemented to meet 21CFR820.30 requirements.

- Creation of a Risk Management Plan and Report (See EN ISO 14971). The requirements for risk management extend over the entire lifecycle of the product, and include requirements for a benefit/ risk assessment. The requirements extend far beyond those of risk analysis.

- Preparation of a Clinical Evaluation Report (CER- see MEDDEV 2.7.1 Rec 3). The CER is a summary of clinical data, defined as the safety and/or performance information that is generated from the use of the device. Clinical Data "are sourced from clinical investigation(s) of the device concerned; or clinical investigation(s) or other studies reported in the scientific literature of a similar device for which equivalence to the device in question can be demonstrated; or published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated."

- If clinical data can be used to demonstrate that clinical performance of your device and the benefits of its use outweigh residual risks, then the CER can be used instead of a clinical investigation to satisfy the clinical requirements of the MDD. If not, the CER is used to identify the specific clinical data that need to be collected in the clinical investigation.

- If CE Marking is obtained without conducting a clinical investigation on the new device, then a Post-Market Clinical Follow-Up Plan will also be required. The plan identifies the proactive procedure to be followed to collect clinical data to demonstrate the residual risks associated with device use remain acceptable. Notified Bodies will not typically accept monitoring of vigilance reports (complaints) to satisfy PMCF requirements. (See MEDDEV2.12/2 rev 2.)

- An Essential Requirements Checklist (ERC) that identifies the requirements of the MDD, the standards applied to meet those requirements, and the documents and reports that identify the specific tests performed and results obtained to meet those standards requirements. Although it is common to demonstrate compliance with standards in 510(k) notifications, it is, for all practical

continues on pg. 3

purposes, required for devices that will be CE Marked.

- Labeling to include symbols (per EN IS0 980, 1041 and 15223) as well as translations (See MEDDEV 2.5/5 Rev 3.), as required.

- A Declaration of Conformity that identifies the catalog numbers of the devices that will be sold in the EU and that are addressed in the technical documents (See NB-MED/2.5.1/Rec5 for information to include in a Technical File).

Of these, the most significant difference lies in the need to create an ERC, as the Essential Requirements identified in the MDD are almost always satisfied by applying standards. Those standards may not typically be addressed in a 510(k) where the major testing effort is expended demonstrating substantial equivalence (comparative safety and efficacy with a predicate device). Note that although the 510(k) process is generally thought of as being unique in that it requires demonstration of "substantial equivalence," demonstrating "equivalence" of your new device with a currently marketed product so that the documented performance of the marketed device can be assumed applicable to your device (See Clinical Data, above) also requires evaluation of "equivalence."

If you already have a CE Marked product and would like to get it cleared for marketing through the FDA's premarket notification process, the following additional tasks will need to be planned for and completed:

- Identification of a suitable predicate device. The predicate device has to be a legally marketed device cleared (or exempt from 510(k) requirements) in the US for the same intended purposes as your new device, and must also employ the same technology. This is not an issue for many devices, but those novel, medium risk Class IIa and IIb devices that are not currently legally marketed in the US will not have a predicate device, triggering the need to file a de novo petition, as well as a 510(k) with the FDA.

- Comparative device testing. Testing conducted to meet standards does not typically include a relative evaluation of safety and performance. Consequently, much of the test data created to meet Essential Requirements is not of use in the 510(k), where substantially equivalent safety and efficacy must be demonstrated to the predicate device.

- Biocompatibility assessments (biological risk evaluations) are viewed much differently by regulatory officials in the EU than by those in the US. Whereas the FDA relies heavily on ISO 10993-defined test results, much of the biological safety information provided in technical files to NBs consists of justifications for not testing, or reports on the use of similar (but not identical) materials. This is great for obtaining the CE Mark, but the FDA often insists on the collection of more test data, especially in the absence of published information on the identical material (processed by the same methods, including sterilization) used in your device.

- Your quality system will have to be certified to ISO 13485 by your Notified Body. Whereas the FDA does not audit your quality system before a 510(k) is cleared, in the most common pathway selected for CE Marking the NB has to issue a quality system certificate in order to CE Mark a Class IIa or Class IIb device.

Of course, the regulatory concerns associated with legally marketing your device in another country may be minor when compared with other business-related obstacles. Sales and distribution networks have to be established, and many countries in the EU will not adopt a new device until a clinical assessment of the device is conducted on their soil. But, regardless of the marketing strategy and product rollout plan, if eventual US and EU distribution is planned, a good deal of time and money can be saved if the device design and development phase is planned to address both US and EU requirements.

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