SurFACTS in Biomaterials

January - February 2010 Volume 15 Issue 1

Materials Reporting Requirements for Medical Devices/Changes in FDA Reviews of Premarket Applications

By Phil Triolo PhD, RAC

Several changes have recently occurred with regulations addressing the use of phthalates and bisphenol A (BPA) in medical devices marketed in the European Union, United States, and Canada. This article reviews the changes in regulations, identifies actions that need to be taken to meet the new requirements, and documents some of the changes manufacturers have seen in the FDA review of their premarket notifications.

Health Canada regulations requiring the Identification of devices that contain phthalates or BPA

Canada's medical device regulatory agency, Health Canada (HC), in response to concerns over the safety of BPA and Phthalates in medical devices and "to allow Canadians to make informed risk management decisions … intends to disclose all licensed medical devices that contain Di(2-ethylhexyl) phthalate (DEHP) or BPA. All manufacturers of licensed Class II, III and IV medical devices [have been] requested to inform Health Canada as to whether their devices contain more than or equal to 0.1% by mass of DEHP or are manufactured from raw materials containing or derived from BPA." See *http://www.hc-sc.gc.ca/dhp-mps/md-im/activit/announce-annonce/md_notice_im_avis_dehp_bpa-eng.php* for details and links. Information that needs to be provided in applications for Class II, III and IV medical devices containing BPA or DEHP is identified in the updated guidance on the preparation of Canadian License applications found at *http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/md-im/*

Materials Reporting Continued on Page 8

Guest Editorial

The Art of Surface Characterization - Enabling a Better BioInterface

The Surfaces in Biomaterials Foundation provides a unique forum for presenting research and development on the "biointerface," the interface between implanted man-made biomaterials and the surrounding human tissue, bone or blood. At the biointerface, knowing which properties of the implant material most strongly influence biocompatibility is critical for optimally designing materials which work well in the human body. By providing important information on the chemical and physical nature of biomaterial surfaces, "surface characterization" enables better biointerfaces.

Surface characterization is the practice of measuring the chemical and physical properties of the outer surfaces of materials, which is mostly science but also includes some practical "art." Since no single instrument measures all the surface properties of interest, successful surface characterization of a biomaterial requires a clear understanding of the critical question(s)

Guest Editorial Continued on Page 2

What's Inside

Guest Editorial
Continued

By Guest Editor Klaus Wormuth, SurModics

to be answered and judicious application of the right instruments and methods to answer the questions at hand. I'm surprised at how often a mismatch occurs between the capabilities of a technique and the questions which need to be answered. Also, I'm surprised at how often (analogous to our health care system!) unnecessary measurements are carried out just because an instrument happens to be available.

In this issue, an article from John Newman of the Evans Analytical Group highlights the tools and the expertise it has available for characterization of biomaterial surfaces. At my company SurModics, we also have invested in optical, scanning electron, Raman, infrared, and atomic force microscopy to measure properties of our medical device coatings and drug delivery technologies. Although expensive, these investments have paid off handsomely in deepening the scientific understanding of our technologies, and in helping to solve problems which arise as products are developed. Also, analogous to the TV series "CSI Miami," surface characterization provides critical information in the investigation of defects and failures in a manufacturing environment.

Thus, surface characterization will be an important component of BioInterface 2010, our annual meeting to be held Oct. 18-20 in Atlanta, GA. BioInterface 2010 welcomes a wonderfully diverse group of engineers, scientists, medical practitioners, regulators and academics to an intimate meeting which focuses on understanding the biointerface. By using surface characterization data to support in vitro and in vivo studies of biomaterials, we strengthen our understanding of the biointerface, advance biomaterials technology, and enable a better BioInterface 2010.

Executive Editor Steven Goodman is on vacation. He will return for the next issue.

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 Right Tool for the Right Job

By John G. Newman, Evans Analytical Group

The old adage of "the right tool for the right job" applies not only in your workshop at home but it applies equally to the analysis of biomedical devices and biomaterials. For cost-efficient problem solving and characterization of biomaterials, the correct analytical tool must be used – one that has the correct depth of analysis, detection range and analytical spot size, and is also applicable to the type of sample being studied.

Questions involving certain materials and processing issues are often very specific and, in turn, these require very specific, and different, analytical tools to provide the correct answers –

- "What has this oxygen plasma done to the surface of my silicone catheter?"
- "Has my cleaning procedure effectively removed the cutting oil on my stainless steel parts and has it left any residue on the surface?"
- "What polymers are used on our competitor's device?"
- "How thick is the polymer coating on my guidewire?"
- "What low level impurities are present in our nitinol raw material?"

Luckily, the toolbox of analytical instruments is very well equipped, with dozens of different methods available for materials characterization, each being very specialized in the type of information it provides. In a pinch, a wrench or some other tool can be used as a hammer; however, in the analytical world, this usually doesn't work. For example, if a relatively deep analysis tool is used for characterizing a sub-monolayer level contaminant, the chances are very slim that the contaminant will actually be identified, or even observed. Likewise, if you want to characterize the bulk of a material, results from a surface sensitive technique may be misleading, as outer surfaces are often substantially different than the bulk.

Figures 1 and 2 on the next page show important parameters for how analytical tools can be classified and ultimately how the correct tool(s) for the job can be chosen. The first figure (The EAG "Bubble Chart") lists detection range and analytical spot size for a variety of techniques. (See end of article for a list of techniques and their acronyms.) Those techniques above the chart are imaging-only techniques (no concentration information) that can provide spatial resolutions on the angstrom scale. The techniques to the right of the chart are bulk-only techniques (i.e. no spatial resolution) some of which provide detection limits in the part-per-billion to part-per-trillion range! The techniques within the chart have analytical spot sizes and detection ranges defined by the size of their "bubble." Techniques having blue bubbles provide elemental information while those in red can also provide chemical or molecular information.

Often, the problem or material question to be addressed limits the number of techniques that can be successfully applied to solve the problem. For example, if elemental information is needed from a feature that is sub-100nm in size, only Auger Electron Spectroscopy could be used. However, if the sample can be thinned appropriately, Scanning Transmission Electron Microscopy coupled with either Electron Energy Loss Spectroscopy or Energy Dispersive X-ray Spectroscopy could also be applicable. Alternatively, if ppm detection limits and chemical/molecular information are both needed from a very thin organic contamination layer 100µm in diameter, Time-of-Flight Secondary Ion Mass Spectrometry is the only tool that will meet these requirements.

Figure 2 lists the typical depth of analysis for different techniques. The depths of analysis range all the way from the top few atomic layers to many micrometers in depth. So clearly we have "little" hammers and "big" hammers at our disposal.

It is only natural to try to use techniques that are readily available to try to solve as many problems as possible. Unfortunately, this means that common techniques often get used in applications where other techniques are much better suited. In general, analytical techniques having a deeper depth of analysis (µm scale) are much more common than techniques having a very shallow depth of analysis (Å scale) such as Auger Electron Spectroscopy, X-ray Photoelectron Spectroscopy, and Time-of-Flight Secondary Ion Mass Spectrometry. However, device contamination, cleaning efficacy, passivation layer thickness and quality, lubrication, plasma/corona

The Right Tool Continued on Page 4

The Right Tool Continued from Page 3

surface modifications, and polymer additive segregation are all biomaterials issues that involve very thin surface layers. When applying µm-scale depth of analysis tools to these surface applications, it is little wonder that the results are inconclusive!
So, the next time you have a biomaterials characterization issue, make sure you are digging into the right tool box before setting up your scope of work. And stop using a wrench to hammer that nail!

A New Tool in the Tool Box

One of the relatively new tools available to surface analysts is that of the C_{60} "buckyball" ion gun. This add-on to XPS and TOF-SIMS instruments is used to ion beam etch (sputter) organic materials in order to expose subsurface layers, while still retaining the chemical integrity of the organic materials. Traditionally, inert gas ion beams such as argon have been used for ion beam sputtering. However, the use of energetic inert gas beams on polymers and other organics causes substantial degradation of the chemical bonding such that the organic is no longer distinguishable and often appears to be mostly graphitic in nature. C_{60} sputtering has opened the way for a variety of new applications that were previously not possible to address adequately:

- Sputter "cleaning" the surface of organics to remove contamination layers
- Obtaining chemical state information from below the extreme surface of thin layers
- Obtaining chemical state information from interfaces

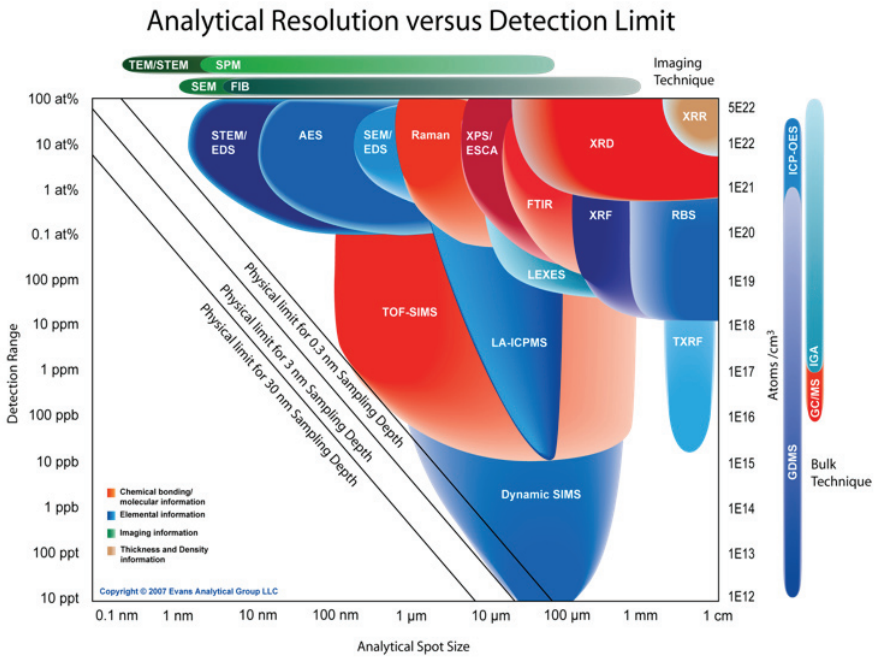


Figure 1. The EAG Bubble Chart

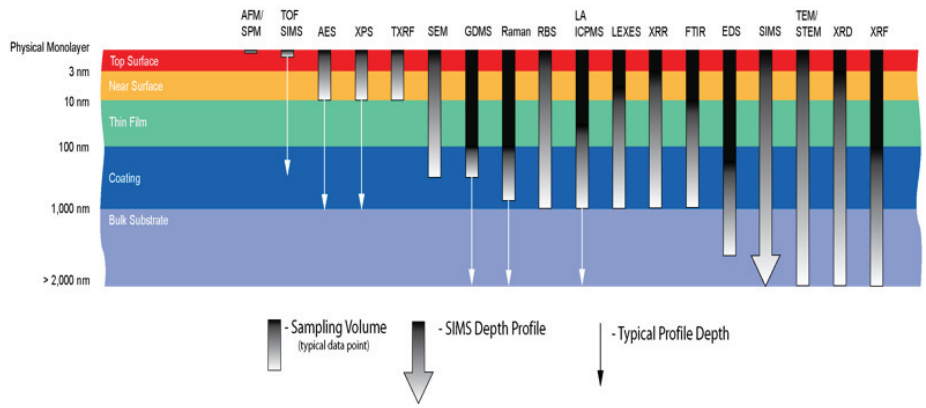


Figure 2. Depth of Analysis Chart

The sputter cleaning aspect of C_{60} is especially useful for TOF-SIMS where even a slight amount of surface contamination can hide species of interest just below the contamination layer. The following example demonstrates the use of XPS C_{60} profiling to clean the surface of a contaminated polymer film and subsequently obtain chemical information characteristic of the bulk of the film.

The XPS analysis of the surface of a lubricious poly(tetrafluoroethylene) (PTFE) film on a metal substrate detected the presence of C, F, and a small amount of O. The carbon peak showed a mixture of primarily hydrocarbon (C-C,C-H) chemistry and a much smaller CF_2 peak (red spectral line in Figure 3). Pure PTFE should show only a CF_2 peak, characteristic of the $-CF_2-CF_2-$ repeat unit. A C_{60} depth profile was then performed to monitor the composition and chemistry with respect to depth. After 1 minute of sputtering (green spectral line), much of the hydrocarbon peak is removed (note the decrease in C-C/C-H peak) with a corresponding

The Right Tool Continued on Page 5

The Right Tool Continued from Page 4

increase in the CF_2 peak. The depth profile (Figure 4) shows that the O is totally removed within a few minutes into the profile. After 20 minutes of sputtering, very little hydrocarbon contamination is observed and the primary signal is that of CF_2 (blue spectral line in Figure 3). At this point the F to C ratio is approximately 2:1 — as it should be for pure PTFE. If this experiment had been performed with an argon ion beam, much of the F on the PTFE surface would have been lost and the carbon spectrum would show no similarity to PTFE.

As the use of C_{60} ion bombardment becomes more common, more and more applications will be developed and it will be especially interesting to see how they apply to the biomaterials industry. Possibilities include following drug distribution with respect to depth and also the study of buried organic interfaces.

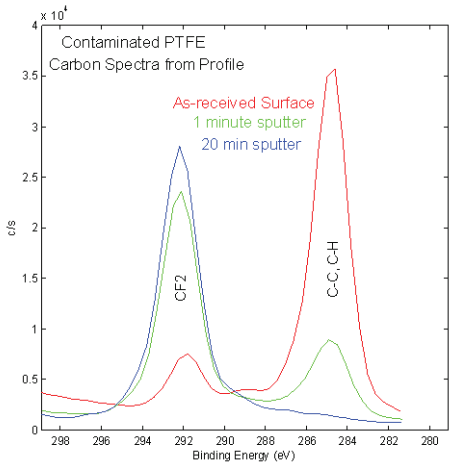


Figure 3. Select carbon spectra from C_{60} depth profile.

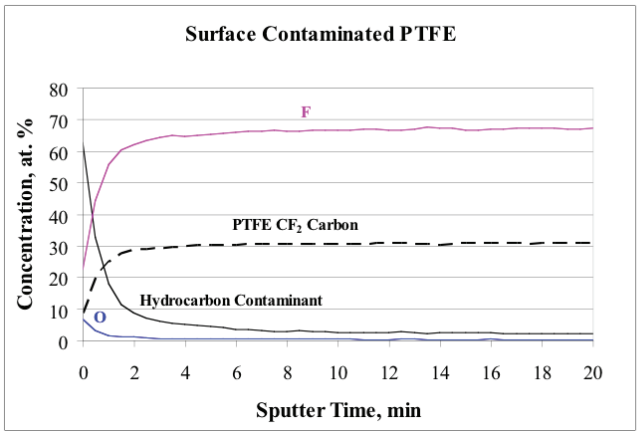


Figure 4. XPS C_{60} depth profile of a contaminated poly(tetrafluoroethylene) (PTFE) thin film.

Analytical Techniques and Their Acronyms

AES	Auger Electron Spectroscopy
EDS	Energy Dispersive X-ray Spectroscopy
EELS	Electron Energy Loss Spectroscopy
FIB	Focused Ion Beam
FTIR	Fourier Transform Infrared Spectroscopy
GC-MS	Gas Chromatography Mass Spectrometry
GDMS	Glow Discharge Mass Spectrometry
ICP-OES	Inductively Coupled Plasma Optical Emission Spectroscopy
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
IGA	Instrumental Gas Analysis
LA-ICP-MS	Laser Ablation Inductively Coupled Plasma Mass Spectrometry
LEXES	Low Energy X-ray Emission Spectroscopy
NRA	Nuclear Reaction Analysis
PIXE	Particle Induced X-ray Emission
Raman	Raman Spectroscopy
RBS/HFS	Rutherford Backscattering Spectrometry/ Hydrogen Forward Scattering
RTX	Real Time X-ray
SEM	Scanning Electron Microscopy
SIMS	Secondary Ion Mass Spectrometry
SPM/AFM	Scanning Probe Microscopy/Atomic Force Microscopy
(S)TEM	(Scanning) Transmission Electron Microscopy
TGA/DTA	Thermogravimetric Analysis/Differential Thermal Analysis
TOF-SIMS	Time-of-Flight SIMS
TXRF	Total Reflection X-ray Fluorescence
XPS/ESCA	X-ray Photoelectron Spectroscopy/Electron Spectroscopy for Chemical Analysis
XRD	X-ray Diffraction
XRF	X-ray Fluorescence
XRR	X-ray Reflectivity

Author: John G. Newman, Director of Analytical Services
Evans Analytical Group, Chanhassen, MN
jnewman@eaglabs.com
www.eaglabs.com

New Year but Questions Remain About Changes at FDA

By Ronald S. Warren, Medical Device Consultants Inc.

As we enter 2010, much uncertainty remains about how personnel and policy changes at FDA and CDRH may impact the medical device industry. In 2009, there were a number of shifts at the agency that could transform the regulatory landscape for device and diagnostic manufacturers in the United States.

First and foremost was the appointment of Margaret Hamburg, MD, as FDA commissioner. In her first year at the head of the agency, she has highlighted the need for improved food safety and has promised increased enforcement and faster agency action for device violations. Moreover, she has publically stated that CDRH has had significant troubles and that big changes are in order for the device review process. Some of the CDRH troubles stem from the controversy related to the 510(k) approval of a knee-repair device. Claiming that the scientific review of this application had been compromised, disgruntled CDRH employees wrote to Congress asking for an investigation into potential industry influence. Later in the year, former Commissioner von Eschenbach admitted that FDA was under undue pressure and influence in the ReGen Menaflex 510(k) clearance. In the shadow of this controversy, long-time CDRH director Dan Schultz resigned and has been replaced with Acting Director Jeffrey Shuren.

Under new leadership, FDA has promised to evaluate the decision-making process with CDRH, and, in particular, the policies and process related to 510(k) reviews. The agency has engaged the Institute of Medicine to perform an audit of the 510(k) process, a $1.3-million program underway through 2011. The aims of this audit are to focus on postmarket research, to increase transparency and to establish clear procedures to resolve differences in FDA decision making. Furthermore, the agency has initiated its own internal review of the 510(k) process, and ODE Director Donna Bea-Tillman has asked device branch chiefs to flag devices that raise new questions of safety and effectiveness or have new intended uses.

In addition to changes within FDA, there are significant external forces that may result in other changes. For example, early in the year the General Accounting Office reported that the 510(k) program was inappropriately used to clear hundreds of products. Last year, Congress called for FDA to finalize classifications on pre-amendment devices, and the House and Senate held hearings on the device review process. Legislatively, there are pending bills related to food safety and possible changes in preemption rules related to device liability laws.

It was a distressing year for the agency. In my view, these changes have created ongoing challenges for companies seeking to get clear guidance on timely approvals of product premarket applications. The implications for 2010 include a slowdown in some reviews and requests for information by review staff particularly for devices with new intended uses or technological characteristics. Industry should also expect to see more enforcement action, particularly for postapproval obligations and in areas where the agency has employed "enforcement discretion" (molecular diagnostic tests, for example). In the longer term, devices are more likely to be classified upward—PMA instead of 510(k)—where there are no clear predicate devices or where there is an expansion of claims and intended use.

The ongoing issues at FDA will take some time to play out. In the meantime, companies are well advised not to "push the envelope" on product claims or ignore their postapproval obligations. Companies with innovative products should take advantage of early collaboration meetings (i.e., pre-IDE process) with CDRH. It will not be surprising if we see a trend in premarket applications requiring more clinical data for Class II devices, and more PMA applications required for innovative or higher risk products. While the coming year will likely result in more industry frustration, companies can benefit from careful regulatory planning and early communication with CDRH on product submissions.

Ronald S. Warren is a principal consultant in the regulatory services group at MDCI, a full-service CRO and regulatory consulting firm focused on the medical device industry. He has more than 22 years of regulatory and clinical affairs experience, with specific expertise in IVD products, human-derived tissue-engineered products, and cardiovascular devices. He has coordinated and led multiple pre-IDE meetings and been involved in the submission and preparation of PMAs, 510(k)s, PMA supplements and IDEs for various clinical indications. Find out more about the company by viewing its listing in the Consultants Directory (www.devicelink.com/consult/m/m019.html) or by going to its website (www.mdci.com).

U.S. Medical Research Funding Falls: Analysis

From Reuters

Public and private funding for U.S. biological and medical research has slowed and resources from one major federal source shrank when inflation is taken into account.

Industry was the largest contributor to biomedical research, accounting for 58 percent of all 2007 spending, the team at the University of Rochester Medical Center in New York found.

They said their findings suggest a more cautious future for medical research, one in which new scientists shy away from risky undertakings that could deliver breakthroughs in favor of safer but less exciting approaches.

The U.S. National Institutes of Health was the second-largest source, paying for 27 percent, they reported in the Journal of the American Medical Association. But funding fell in real terms.

"After a decade of doubling, the rate of increase in biomedical research funding slowed from 2003 to 2007, and after adjustment for inflation, the absolute level of funding from the National Institutes of Health and industry appears to have decreased by 2 percent in 2008," the report reads.

Rochester's Dr. Ray Dorsey and colleagues looked at a variety of sources to calculate the total amount of public spending on biomedical research, mostly from the National Institutes of Health, and private sources like pharmaceutical, biotechnology and medical device firms.
They found total funding rose from $75.5 billion in 2003 to $101.1 billion in 2007, an increase of 14 percent when adjusted for inflation. However, it stalled the next year and could be hit hard by the global recession, they said.

Funding from NIH and private industry was $86.4 million in 2007 and $88.8 billion in 2008. But when the 2007 number is adjusted for inflation, this represents a 2 percent decrease, they said.

"Biomedical research captures the public's imagination," they added. It also leads to economic development, they said.

"Therefore, in the coming years, debate will likely increase between those who view technology as a source of additional cost and those who view it as a source of value. The research community should be mindful of how others view it and take aggressive steps to enhance its own productivity."

Additionally, researchers may avoid risky experiments in a conservative environment, they said. "It makes them cautious and may portend a trend to favor incremental research rather than high-risk/high-reward avenues, which have particular value to refractory diseases and those of great clinical or public health impact," they wrote.

The issue is not trivial and it is the subject of political debate. "In 2007, the United States spent an estimated 4.5 percent of its total health expenditures on biomedical research and 0.1 percent on health services research," the researchers wrote.

In September, President Barack Obama announced a plan to spend $5 billion from the $787 billion economic stimulus package on medical and scientific research.

Materials Reporting Continued from Page 1

md_gd_licapp_im_ld_demhom-eng.pdf.
If you haven't yet reported this information, or if you are preparing to license a device in Canada, the relevant information must be provided. HC has indicated that it has no current plans for use of this information; it only wants to be made aware of the devices that contain these substances. See, e.g. http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/md_qa_im_qr_dehp_bpa-eng.php It should be noted, however, that HC recently banned the use of a number of phthalates at concentrations higher than 0.1% in children's toys, and future regulation of the content of these phthalates in medical devices cannot be ruled out.

Canada's nearest neighbor, meanwhile, has recently updated its assessment of the health effects of BPA. On January 15, the US FDA issued a statement on its assessment of the presence of BPA in containers for food, especially those containing baby food and infant formulas. The statement can be found at http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm197739.htm.

FDA's "Current Perspective on BPA": "At this interim stage, FDA shares the perspective of the National Toxicology Program that recent studies provide reason for some concern about the potential effects of BPA on the brain, behavior, and prostate gland of fetuses, infants and children. FDA also recognizes substantial uncertainties with respect to the overall interpretation of these studies and their potential implications for human health effects of BPA exposure. These uncertainties relate to issues such as the routes of exposure employed, the lack of consistency among some of the measured endpoints or results between studies, the relevance of some animal models to human health, differences in the metabolism (and detoxification) of and responses to BPA both at different ages and in different species, and limited or absent dose response information for some studies.

"FDA is pursuing additional studies to address the uncertainties in the findings, seeking public input and input from other expert agencies, and supporting a shift to a more robust regulatory framework for oversight of BPA to be able to respond quickly, if necessary, to protect the public.

"In addition, FDA is supporting reasonable steps to reduce human exposure to BPA, including actions by industry and recommendations to consumers on food preparation. At this time, FDA is not recommending that families change the use of infant formula or foods, as the benefit of a stable source of good nutrition outweighs the potential risk of BPA exposure."

It is probable that the FDA will evaluate the potential toxicity of BPA when it is present in medical devices used in applications that could affect fetuses, infants and children and issue its conclusion, but it is anticipated that the results of this evaluation will not be available this year.

Recent amendment of the Medical Devices Directive require labeling of certain devices that contain phthalates which are classified as carcinogenic, mutagenic or toxic to reproduction of category 1 or 2 in accordance with table 3.2 of Annex VI of Regulation 1272/2008, **Classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.** Per the consolidated Medical Devices Directive 93/42/EEC, as amended by Directive 2007/47/EC, if any of these phthalates are part of the formulation and a device is:

a) intended to administer and/or remove medicines, or
b) intended to administer and/or remove body liquids, or
c) intended to administer and/or remove other substances to or from the body, or
d) intended for transport and storage of such body fluids

it shall be marked on the device itself and/or on the packaging for each unit or, where appropriate, on the sales packaging with a symbol identifying the phthalate(s) present. The particular phthalates so classified are bis (2-ethylhexyl) phthalate (DEHP); benzyl butyl phthalate (BBP) and dibutyl phthalate (DBP).

Each of these phthalates, commonly used to plasticize poly(vinylchloride) (PVC) medical tubing, must be identified to the end user per section 7.5 of Annex I of consolidated Directive 93/42/EEC, whose requirements begin to be phased in on 21 March 2010 (See Implementation of Directive 2007/47/EC Amending Directives 90/385/EEC,

Materials Reporting Continued on Page 9

Materials Reporting Continued from Page 8

93/42/EEC and 98/8/EC: http://ec.europa.eu/enterprise/sectors/medical-devices/files/guide-stds-directives/transitionalperiod_2007-47-ec_guidance_final_en.pdf).

Unfortunately, although there is a requirement that the EU provide a symbol to be used to identify the presence of the potentially toxic phthalates, none has yet been approved. However, pr EN 15986, Symbol for use in the labelling of medical devices, a draft harmonized standard that is currently circulating for approval, presents a series of symbols that will, most probably, be adopted and are therefore the best available symbols to incorporate into labeling. The primary symbol is an equilateral triangle with its apex pointing downward, containing the letters "PHT" with a meaning of "contains or presence of phthalate". Accompanying the phthalate symbol is an abbreviation for one or more of the phthalates that is present- "DEHP", "DBP" or BBP". Under the proposed EN standard, the specific phthalate(s) have to be present in order to be identified. That is, it would not be permissible to use a single universal phthalate label that identifies the presence of DEHP or DBP or BBP as a "catch all" for all devices containing potentially toxic phthalates.

Per MDD Essential Requirement (ER) 7.5 , Leakage, "The devices must be designed and manufactured in such a way as to reduce to a minimum the risks posed by substances leaking from the device…" and, "If the intended use of such devices includes treatment of children or treatment of pregnant or nursing women, the manufacturer must provide a specific justification for the use of these substances with regard to compliance with the essential requirements, in particular of this paragraph, within the technical documentation and, within the instructions for use, information on residual risks for these patient groups and, if applicable, on appropriate precautionary measures."

From a practical standpoint, an analysis of the risks associated with phthalate use in devices intended for the uses identified above has to be performed. The expectation is that, as soon as a less-toxic substitute for a potentially toxic phthalate is available, it will be used. This expectation is outlined in a memo written by the UK's MHRA (Medicines and Healthcare products Regulatory Agency) whose position is that the application of risk analysis under the MDD is sufficient to assure that the potentially toxic phthalates are replaced by non-toxic alternatives. See http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Technicalinformation/PhthalatesinPVCmedicaldevices/index.htm. Presumably, the only acceptable reason for the continued marketing in the EU of a device containing a potentially toxic phthalate is that another plasticizer with suitable physical properties and less potential toxicity is unavailable.

Independently, the US FDA has conducted a safety assessment and identified specific procedures utilizing devices or systems that contain levels of phthalates and exposure periods to allow potentially dangerous levels of phthalates to be leached into sensitive patients. See http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM080457.pdf. The list of procedures includes:

- IV infusion of crystalloid fluids and drugs
- Total Parenteral Nutrition (TPN)
- Blood transfusion
- Cardiopulmonary bypass and ECMO
- Hemodialysis and peritoneal dialysis
- Enteral nutrition and breastfeeding
- Aggregate exposure to DEHP from multiple medical devices

Per US FDA recommendations found at http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm062182.htm, "Most importantly, you should not avoid the procedures cited above simply because of the possibility of health risks associated with DEHP exposure. The risk of not doing a needed procedure is far greater than the risk associated with exposure to DEHP." That is, the FDA has concluded that the benefits derived from the use of devices containing phthalates outweigh the potential risks associated with the leaching of phthalates.

However, per the new MDD requirements, the instructions for use and technical documentation have to identify residual risks associated with the leaching of the suspect phthalates into devices used by the at-risk patient groups, and, if necessary, precautionary measures to take to minimize the risks.

Given that any coating present on a device containing phthalates potentially acts as a barrier to diffusion, it is

Materials Reporting Continued on Page 10

Materials Reporting Continued from Page 9

not surprising that study results have shown that the levels of phthalates released from heparin-coated devices are lower than those released from uncoated controls. (See the FDA Safety Assessment, referenced above.) So, there is a potential for promoting heparin-coated devices that contain phthalates because of this advantage, as long as suitable supporting data have been collected.

The method for assaying heparin potency prescribed in the USP Heparin Monograph has recently changed. Heparin assayed by the new method will be assigned a potency higher than that assigned by the "old" USP method. Consequently, the labeled potency of heparin solutions may have to be changed, or more heparin may have to be added to a solution in order to achieve the desired clinical effect. Note that the change is only for unfractionated heparin, and that the effectiveness of heparin-coated devices isn't affected as long as appropriate changes are made in specifications for the heparin. Details and links to additional information are provided in a FDA Health Alert that can be accessed at *http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm184502.htm* .

Many folks have asked **what can be expected from the FDA with respect to the product clearance/ approval process.** I asked my clients if they've seen any differences in the review process or time frames. They report that, in general, review times for traditional 510(k) notifications have been longer, closer to 90 days than 60 days which had been the expected period for receiving an initial response. Reviewer questions have been somewhat unpredictable, which could be predicted given the large number of new FDA investigators that has just been hired. Changes vary from division to division, rather than being uniform across CDRH. With respect to FDA audits, there is an increased scrutiny of medical device reporting activities.

Note that the 510(k) premarket notification process is under review, and some modifications will probably be made. Details of changes have not yet emerged, but an increased reliance on standards is anticipated. Also, FDA Commissioner Hamburg's recent policy statement addressing the need for rapid industry responses to FDA warning letters will require a quicker response than has been expected in the past. See *http://www.fda.gov/NewsEvents/Speeches/ucm175983.htm* .

With respect to coated devices or devices with surface modifications, the biggest concern expressed by manufacturers is that shelf life claims can only be based on real-time aging results; it is difficult to demonstrate a reasonable assurance that antimicrobials do not present an unreasonable risk of inducing resistant organisms. The potential for particulate generation from coated devices has to be evaluated.

If you have had recent experiences with the FDA, Notified Bodies, or other regulatory agencies that would be of interest to the surfaces community, please email them to Phil Triolo at philt@philt.com, and he will include them in upcoming SurFACTS *newsletters without identifying sources.*

Meeting/Conference/Trade Show Calendar

Meeting/Conference/Trade Show	Dates	Place	Web Address
Medical Device Breakfast Series: Company Valuation for M&A	Feb 9	Palo Alto, CA	baybio.org/wt/page/Company_Valuation_For_M_A
Therapeutic Breakfast: Clinical Trials Abroad: Options for Smaller Companies with Limited Funds	Feb 25	Redwood City, CA	http://www.baybio.org/wt/page/Clinical_Trials_Abroad
BayBio NEST: 7th Annual Life Sciences Investor and Entrepreneur Roundtables	Mar 17	Palo Alto, CA	http://www.baybio.org/institute/wt/page/7th_Annual_Life_Sciences_Investor___Entrepreneur_Roundtables
International Symposium on Surface Science Aspects of Pharmaceutical Science, Pharmacology, Cosmetics and Bio-Technology	Apr 19-21	Danbury, CT	mstconf.com/SurfSciPharm.htm

Abbott's XIENCE V® Approved in Japan – Second Largest Drug Eluting Stent Market Worldwide

Abbott recently announced that the Japanese Ministry of Health, Labor and Welfare (MHLW) has approved its XIENCE V® Everolimus Eluting Coronary Stent System for the treatment of coronary artery disease. Japan is the second largest drug eluting stent market in the world after the United States, with approximately 200,000 stent procedures performed each year. The company plans to launch XIENCE V in Japan in the upcoming weeks, immediately following final reimbursement authorization.

"With today's approval, physicians in Japan will now have access to a next-generation drug eluting stent that offers outstanding ease of use and excellent clinical performance and safety. XIENCE V is the ideal combination as documented by the more than 16,000 patients who have been enrolled in the SPIRIT family of trials," said Robert Hance, senior vice president-vascular, Abbott. "Each aspect of XIENCE V's design, from the thin struts to the flexible delivery system to the drug and polymer, was carefully engineered for optimal deliverability and to improve safety and efficacy outcomes for patients compared to earlier generation stents. These attributes have made XIENCE V the market-leading drug eluting stent around the world, and we look forward to making XIENCE V available to physicians in Japan shortly."

"XIENCE V is flexible and easy to deliver through the coronary anatomy to the lesion site. These attributes combined with the strength of the safety and efficacy data supporting it give me confidence that XIENCE V is a true next-generation stent that has the potential to benefit heart patients in Japan," said Shigeru Saito, M.D., F.A.C.C., F.S.C.A.I., F.J.C.C., director, Cardiology and Catheterization Laboratories, Shonan Kamakura General Hospital, and principal investigator for the SPIRIT III Japan Registry.

The outstanding data for XIENCE V includes clinically superior long-term efficacy and safety results in the primary endpoints of the pivotal trials and among the SPIRIT family of trials. The SPIRIT III Japan Registry of 88 patients demonstrated similar angiographic and clinical results to the outstanding outcomes from the SPIRIT III U.S. trial. In the SPIRIT III Japan Registry, XIENCE V demonstrated a single-digit rate of major adverse cardiac events (MACE, 8.0 percent), and no cases of stent thrombosis (blood clots) out to one year. MACE is an important composite clinical measure of safety and efficacy outcomes for patients and is defined as cardiac death, heart attack (all myocardial infarction or MI), or ischemia-driven target lesion revascularization (ID-TLR).

In the SPIRIT III U.S. trial, XIENCE V demonstrated an impressively low rate of very late stent thrombosis with no additional events between two and three years and a 43 percent reduction in the risk of MACE compared to the TAXUS® Express2 Paclitaxel-Eluting Coronary Stent System (TAXUS) at three years (9.1 percent for XIENCE V vs. 15.7 percent for TAXUS, p-value=0.003).

In SPIRIT IV, one of the largest randomized trials comparing two drug eluting stents, XIENCE V demonstrated a statistically significant 39 percent reduction in target lesion failure (TLF) compared to TAXUS at one year (3.9 percent for XIENCE V vs. 6.6 percent for TAXUS, p-value=0.0008). TLF is a composite measure of important efficacy and safety outcomes for patients and includes cardiac death, target vessel MI and ID-TLR. XIENCE V also had an exceptionally low rate of stent thrombosis out to one year, with a 74 percent reduction in definite/probable stent thrombosis per the Academic Research Consortium (ARC) definition compared to TAXUS (0.29 percent for XIENCE V and 1.10 percent for TAXUS, p-value=0.004).

Additionally, in the investigator-initiated COMPARE trial of real-world patients, XIENCE V demonstrated significantly better outcomes in key safety and efficacy measures compared to the TAXUS® Liberte Paclitaxel-Eluting Coronary Stent System (TAXUS). At one year, XIENCE V demonstrated a statistically significant 31 percent reduction in MACE compared to TAXUS (6.2 percent XIENCE V vs. 9.1 percent TAXUS, p-value=0.023) and a statistically significant 74 percent reduction in stent thrombosis compared to TAXUS (0.7 percent XIENCE V vs. 2.6 percent TAXUS, p-value=0.002). In the COMPARE trial, MACE is defined as all death, non-fatal MI and target vessel revascularization.

XIENCE V Approved in Japan Continued on Page 12

Major Health Care Reforms in China Supported Growth of More Than 20% in the Drug-Eluting Stent Market in 2009, According to Millennium Research Group

From PRNewswire

According to Millennium Research Group (MRG), the global authority on medical technology market intelligence, health care reforms in China supported rapid expansion of the Chinese drug-eluting stent market in 2009 and will continue to fuel growth in the coming years. MRG's new Asia Pacific Markets for Interventional Cardiology Devices 2010 report finds that initiatives undertaken by the Chinese government will allow the Chinese drug-eluting stent market to reach a value of more than $900 million by 2014.

The potential Chinese patient population for coronary stenting has historically been underpenetrated due to the high cost of the devices. Despite a rising incidence of coronary artery disease in the country, many patients choose to forego a coronary intervention due to a lack of insurance coverage and an inability to privately finance these procedures. In April 2009, the Chinese government unveiled its plans for a universal health care plan, a component of part of its Healthy China 2020 plan, which was first announced in January 2008. The healthcare reforms will increase access to premium-priced procedures and have huge implications for the drug-eluting stent market.

"This amount of funding earmarked for a public health care system will vastly expand the volume of drug-eluting stent procedures performed in China," says Dan Whalen, Analyst at MRG. "With more people able to afford the procedure, this market is expected to grow an average of nearly 20% per year over the next five years, which presents a huge opportunity for new and emerging drug-eluting stent manufacturers in the region."

MRG's new report, Asia Pacific Markets for Interventional Cardiology Devices 2010, provides critical insight into trends that will fuel market growth for coronary stents, PTCA balloon catheters, and accessory devices through 2014. In addition to China, the report also includes analyses of Australia, India, and South Korea. With detailed analysis of procedures, units, average selling prices, revenues, and competitive dynamics, this report will allow readers to trace current and emerging market trends, identify opportunities, and track competitors.

XIENCE V Approved in Japan Continued From Page 11

More About XIENCE V

Abbott's market-leading XIENCE V is used to treat coronary artery disease by propping open a narrowed or blocked artery and releasing the drug, everolimus, in a controlled manner to prevent the artery from becoming blocked again following a stent procedure.

XIENCE V is built upon Abbott's market-leading bare metal stent, the MULTI-LINK VISION® Coronary Stent System. The VISION platform is designed to facilitate ease of delivery, making it easier for physicians to maneuver the stent and treat the diseased portion of the artery.

In some geographies, Abbott supplies a private-label version of XIENCE V to Boston Scientific called the PROMUS® Everolimus-Eluting Coronary Stent System. PROMUS is designed and manufactured by Abbott and supplied to Boston Scientific as part of a distribution agreement between the two companies.

Everolimus, developed by Novartis Pharma AG, is a proliferation signal inhibitor, or mTOR inhibitor, licensed to Abbott by Novartis for use on its drug eluting stents. Everolimus has been shown to inhibit in-stent neointimal growth in the coronary vessels following stent implantation, due to its antiproliferative properties.

XIENCE V is used to improve coronary luminal diameter in patients with symptomatic heart disease due to de novo native coronary artery lesions (lesions less than or equal to 28 mm). Additional information about XIENCE V, including important safety information, is available online in Japanese at www.xiencev.jp, and in English at www.xiencev.com or www.abbottvascular.com/en_US/content/document/eIFU_XienceV.pdf.

Medtronic to Acquire Invatec and Affiliated Companies

Acquisition Will Expand Product Offering and Pipeline for Cardiovascular Interventions

From Medtronic

Moving to expand its impact on peripheral vascular disease, Medtronic, Inc. announced that it has signed a definitive agreement to acquire Invatec, a developer of innovative medical technologies for the interventional treatment of cardiovascular disease, and two affiliated companies: Fogazzi, which provides polymer technology to Invatec; and Krauth Cardiovascular, which distributes Invatec products in Germany. The agreement calls for Medtronic to make an initial payment of $350 million to Invatec and additional payments of up to $150 million for Invatec's achievement of specific milestones.

Invatec's array of stents, angioplasty balloons and accessory products complement therapies and products in Medtronic's CardioVascular business, adding a robust peripheral franchise and pipeline, while enhancing its coronary product offering. Notably, Invatec has brought four drug-eluting balloons to market, covering the coronaries and lower-extremity vessels – the only company worldwide with this distinction. It is a pioneer in the development and commercialization of lesion-specific solutions, including therapies for below-the-knee and carotid artery disease.

"Medtronic's acquisition of Invatec will accelerate the growth of our CardioVascular business, adding important new products for the coronary and peripheral vascular markets," said Scott Ward, senior vice president at Medtronic and president of the CardioVascular business.

"Invatec brings to Medtronic an established international business with a European center of technology development and manufacturing, as well as a strong history of delivering products and high-value solutions to the interventional market," said Andrea Venturelli, co-founder, chief executive and technical officer of Invatec. Invatec co-founder Stefan Widensohler, vice president of global sales and marketing, said, "Our integration into Medtronic creates a tremendous opportunity to leverage Medtronic's global scale and scope across geographies and functions, from R&D to sales and marketing, to advance the interventional treatment of cardiovascular disease."

Cardiovascular interventions represent the world's largest sector of the medical device market, generating $10 billion annually on a global basis. A significant growth opportunity within this sector is peripheral vascular disease, a large and underserved market currently estimated at $2 billion annually and growing faster than 10 percent per year. Approximately 20 million people in the United States and Western Europe alone suffer from peripheral vascular disease, which causes pain, reduces mobility, inhibits wound healing and leads to approximately 250,000 amputations per year. Together, Medtronic and Invatec will be better positioned to address these and other unmet clinical needs in the treatment of cardiovascular disease, the world's leading cause of death.

About Invatec

Invatec *(www.invatec.com)* is an innovator in the development and commercialization of interventional coronary and peripheral products, with global headquarters in Europe. Driven by research and technology, Invatec actively collaborates with physicians and centers of excellence to develop products that will improve life expectancy and quality of life for patients. The company's core competencies include polymer processing, metallurgy, surface treatments and drug coatings. Invatec is vertically integrated with full in-house capabilities to design, develop, manufacture and assemble its 35 product families currently offered in more than 70 countries. Dedicated to "making ideas come alive," the company was founded in 1996 by Andrea Venturelli and Stefan Widensohler, and employs approximately 900 people, predominantly in Brescia, Italy, and Frauenfeld, Switzerland.

Wanted: Members

To be leaders in the surface science community

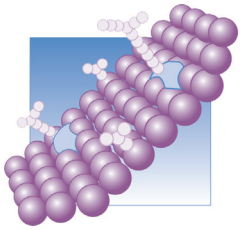
- Join a forum that fosters discussion and sharing of surface and interfacial information
- Have your voice heard and your interests represented within the surface science and biomedical community
- Help shape workshops and symposia that further the world-wide education of surface science
- Promote understanding of interfacial issues common to researchers, bio-medical engineers and material scientists.

Benefits of Membership:

- Discounted registration at BioInterface, the annual symposium of the Surfaces in Biomaterials Foundation.
- Your logo and a link to your Web site in the member directory on the official Web site of the Foundation, www.surfaces.org.
- Complimentary full page ad in surFACTS, the Foundation's newsletter and discounts on all advertising.

Join the Foundation that connects the academic, industrial, and regulatory committees within the surface science/biomedical communities!

Visit the Foundation at www.surfaces.org for a membership application or call 651-290-6267.



Surfaces in ***Biomaterials*** Foundation

Thank You to Our Members!

Abbott Vascular

AST Products, Inc.

Bausch & Lomb

BD

Biocoat Incorporated

Boston Scientific

MRI Network
Capstone Search Group
Building the Heart of Business™

carmeda
A Subsidiary of W. L. Gore & Associates

Covidien

csm Instruments

DePuy
a Johnson & Johnson company

DSM PTG, Inc.
Part of DSM Biomedical

EAG
Evans Analytical Group

genzyme

GORE
Creative Technologies Worldwide

Harland Medical Systems

Hysitron, Inc.
Nanomechanical Test Instruments

Lifecore Biomedical

Medtronic
When Life Depends on Medical Technology

Physical Electronics

qsense

Surface Solutions
Laboratories Incorporated

Coatings2Go
An affiliate of Surface Solutions Labs, Inc.

SurModics

MDEC
Medical Device
Evaluation Center

University of Louisville and Jewish Hospital
Cardiovascular Innovation Institute

University of Minnesota