OFFICE OF SCIENCE AND TECHNOLOGY

Annual Report

Fiscal Year 1999

October 1, 1998 – September 30, 1999

May 2000

Food and Drug Administration
Center for Devices and Radiological Health

PREFACE

The Office of Science and Technology (OST) is the laboratory of the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration.

The Office of Science and Technology (OST) supports the scientific basis for the Agency's regulatory policies through development of independent laboratory information for regulatory and other public health activities of the Center for Devices and Radiological Health (CDRH). OST accomplishes this mission by managing, developing, and supporting standards used for regulatory assessments; performing laboratory evaluations and analyses in support of CDRH premarket and postmarket activities; developing data needed for current and future regulatory problems; and performing research, anticipating the impact of technology on the safety, effectiveness, and use of regulated products.

Specifically, OST develops and conducts research and testing programs in the areas of physical, life, and engineering sciences related to the human health effects of radiation and medical device technologies. It provides expertise and analyses for health-risk assessments. The Office also develops new or improved measurement methods, techniques, instruments, and analytical procedures for evaluating product performance and reliability. OST provides innovative solutions to public health problems through the development of generic techniques to enhance product safety and effectiveness. The laboratory activities of the Office have four major focus areas: characterization of the constituents or components of products; measurement of product performance; bioeffects which derive from human exposure to radiation or medical devices; and radiation metrology in support of Agency regulation of radiation-emitting products.

The purpose of the OST Annual Report is to update our readers about OST's organization, staffing, and intramural science activities; provide a summary of our direct lab support for pre-market review and compliance cases; and provide a bibliography of scientific publications, presentations, contracts, patents, and research seminars of the Office for 1998. The Annual Report is an overview rather than a comprehensive accounting. For additional information, please contact us. The Report might also be viewed as a source of information regarding areas in which Cooperative Research and Development Agreements (CRADAs) can be initiated with interested institutions. Comments are welcome on the programs described in this report. We hope you find this report useful and informative, and we invite any comments you might want to offer.

Donald E. Marlowe
Director
Office of Science and Technology

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October 1, 1998 – September 30, 1999

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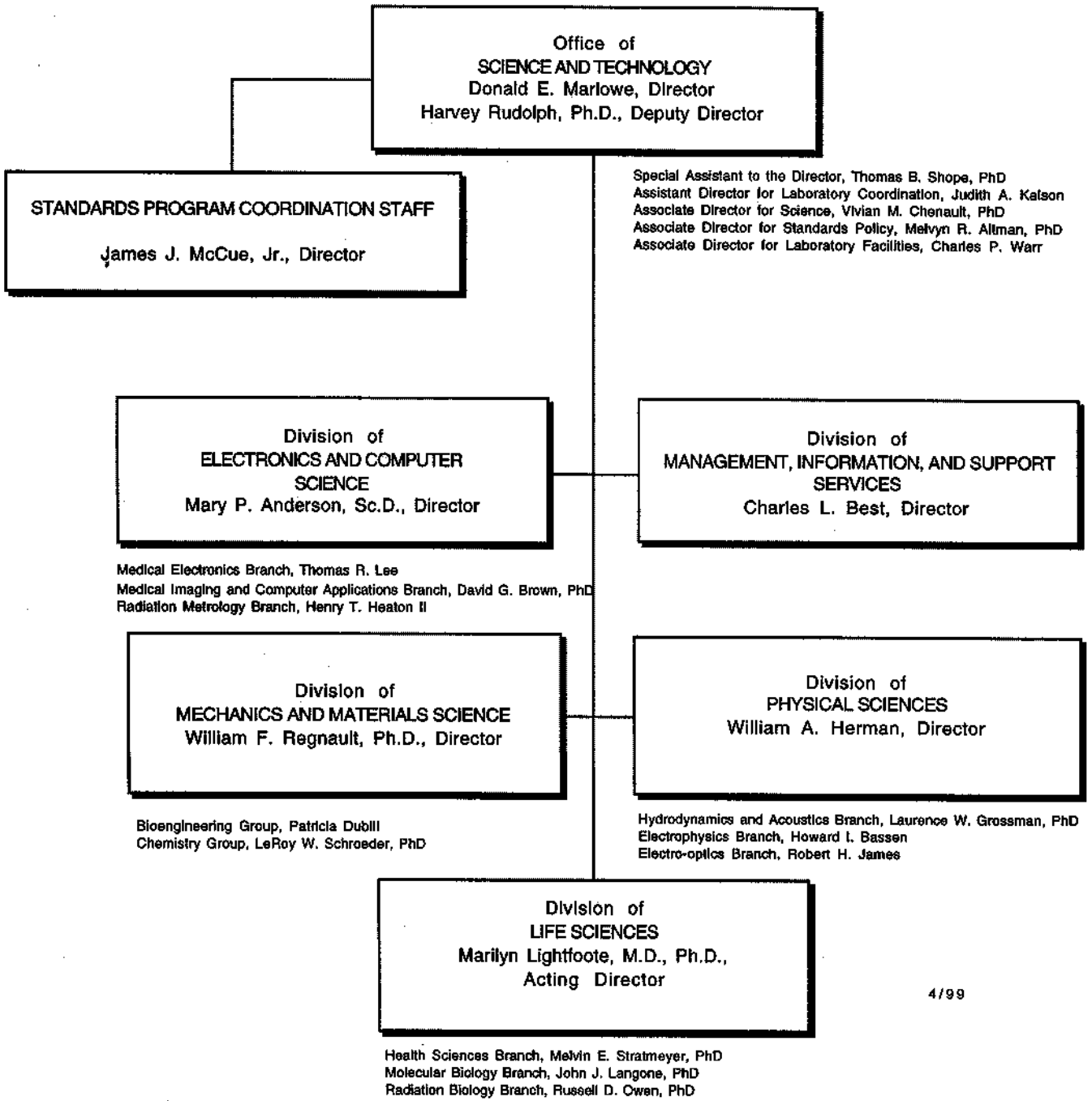
OFFICE OF SCIENCE AND TECHNOLOGY
Organization Chart



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INTRODUCTION

The Office of Science and Technology (OST) is the laboratory of the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration. OST supports the scientific basis for the Agency's regulatory decision making through development of independent laboratory information for regulatory and other public health activities of the Center for Devices and Radiological Health (CDRH). OST accomplishes this mission by working in four areas: managing, developing, and supporting standards used for regulatory assessments; providing technical consultations and performing laboratory evaluations and analyses in support of CDRH pre-market and post-market activities; developing forensic data needed for current and future regulatory problems; and performing research, anticipating the impact of technology on the safety, effectiveness, and use of regulated products. In this section of the OST Annual Report these activities will be summarized and a few highlighted.

TECHNICAL CONSULTATIONS

The organization of OST is structured along technical department lines, similar to the organization of university departments of expertise, in contrast to the organization of the Offices of Device Evaluation (ODE) and Compliance (OC), which are organized along business lines. This enables the other Offices of the Center to identify and use specific expertise solving problems or consulting on the various regulatory functions of the Agency. These "bread-and-butter" activities of the Office also serve OST staff by placing them in everyday contact with an evolving industry and with the "use-problems" that occur with devices. **Table 1** shows the relative changes in these interactions in the pre-market review area over recent years. One of the areas in which OST can contribute most effectively to the Center's regulatory programs is through contribution to the development of guidance documents, such as guidance to reviewers and manufacturers related to the approval requirements of a specific product. **Table 2** is an illustrative list of these types of consultations for 1999. On occasion, the OST contribution is limited to developing and validating an appropriate test method for determining a specific piece of information needed for a particular device. **Table 3** is a list of these types of efforts in OST this year. OST receives many requests to provide expertise and information which cannot be characterized into any of the above tables. **Table 4** is a summary of the requests from the Center, and **Table 5** is a summary of requests from non-CDRH sources. Finally, OST contributes to the Center's active postmarket surveillance activities. **Table 6** is a summary of those activities performed in fiscal year 1999.

Table 1 – Premarket Review – Technical Consultations

	1996	1997	1998	1999
IDE & Supplements	64	106	182	202
PrePMA, PMA & Supplements	42	88	156	169
510(k)	65	125	146	134

Table 2 – Premarket Review – Significant Contribution as an Author of New or Revised Guidance

SOP for the Identification and Evaluation of Candidate Consensus Standards for Recognition
In-Vivo Electro-optical Devices for the Detection of Cervical Cancer and its Precursors
Implanted Cardioverter Defribrillator
Off-the-Shelf Software
Cervical Cancer Detection
Needle disposal Devices
Endometrial Ablation
Low Energy Brachytherapy Sources
Radionuclide Dose Calibrators
Expiration Dating of Natural Rubber Latex Medical Gloves
Adhesion Barriers
Implantable Breast Prosthesis
Exhaustive Extraction of Polymers
Diagnostic Ultrasound
Non-Automated Blood Pressure Cuffs
Non-Invasive Blood Pressure Monitor
Prosthetic Heart Valves
Optical Diagnostic Instruments – Cervical Cancer
Optical Diagnostic Instruments – Ophthalmic Instruments
Wireless Medical Telemetry
Angioplasty Ring
Testing of Skin Sensitization to Chemicals in Latex Products
Endoscope Sheaths
Condoms
Digital mammography
Immunotoxicity

Table 3 – Premarket Review – Guidance Test Method Development or Evaluation

Shelf Life Testing of Medical Gloves

Table 4 – Premarket Review – Miscellaneous Contributions

Reuse of Single Use Devices
- Steering Committee
- Policy Committee
- Research Agenda

PDP Review
Encore Inc.
Pulsarmax Pacemaker
Morphometrix CYMET Screen
TEPRSSC
EAS and Metal Detection Systems
Wireless Medical Telemetry
Personal Screening System
CT Fluoroscopy
Sunlamp Performance Standard
Y2K Activities
- Center Focus Person
- Center Working Group
- Agency Working Group
- Congressional Testimony

Working Group for Evaluation of the DIASENSOR Blood Glucose Monitor
Working Group for Cygnus Glucowatch
Working Group on Regulation of Glove Powder
Working Group on Apnea Monitor Standard
Working Group on Dioxin Risk Assessment
Expiration Dating Working Group
NIH/DOE RAPID ELF/EMF Exposure Facility
Reengineering
- Postmarket
- Radiological Health

Biomaterials Group
Biomaterials Compendium
Bone Sonometry
Toxicology Working Group
IMMUNOTOX on-line services for FDA reviewers
ICCVAM Working Group – LLNA Assay
DCRND Clinical Trial Board
FDA/SCVIR Forum (Chairperson)

Table 5 – Technical Consultations for Non-CDRH Clients

Software Policy Task Force – FDA
FDA/USP Steering Committee – FDA
FY2001 Budget Committees - FDA
    Research
    Standards
Review of California Prop 65 Chemicals - FDA
Breast Disease Diagnosis Coordinating Group – FDA/NCI
Manufacture of illegal ultrasound scanheads – FDA/OCI &DOJ
Photosciences Network Study – FDA/OS
Laboratory Accreditation Committee – FDA/OS
Design of laboratory for Toxicology Testing – FDA/NCTR
Wells Johnson Ultrasonic Aspiration Device – FDA/ORA/Tucson
Contamination of Dialysis Acid with compressor Oil – FDA/ORA/New Jersey
Sunscreen Monograph – Review of FR Notice – FDA/CDER
Spectral measurement of solar simulator – FDA/CDER
Characterization of Solar Simulator for Photocarcinogenesis Testing – FDA/CDER
Source Characterization of solar simulator – FDA/CDER
DUROS Leuprolide Implant – FDA/CDER
Adverse Effects of Mercury-containing Products – FDA/CDER
Mercury in Over-the-Counter Drugs and Products – FDA/CDER
Blood Bank Software Reviews – FDA/CBER
Plasticizers in Blood Bag Meeting Steering Committee – FDA/CBER
Biologic Instruments Software Reviews – FDA/CBER
HemaSure Leukoreduction Filter – FDA/CBER
Circe Biomedical Artificial Pancreas – FDA/CBER
Software Review support – FDA/CBER
Clinical Software Guidance – FDA/CBER
IR-emitting veterinary devices – FDA/CVM
Dioxin in animal feed – FDA/CVM
Virtual Trials Exercise (VT-2) – USUHS
Phthalates Interagency Committee
Canadian Ultrasound Guidance – HPB Canada
Regulation of Diagnostic Ultrasound Devices – Gov't of Philippines
Software Design support – USA/Walter Reed
Review of grant proposal for Ceramics – NSF
Review of SBIR Proposals – NSF
Co-organizer for Workshop on coating Metrology – NIH
Planning Committee for Workshop on Implant Retrieval – NIH
Diagnostic Imaging Study Section – NIH
Diagnostic Imaging Study Section SBIR – NIH
Muscular, Skeletal, and Dental Study Section SBIR - NIH
Report to Congress on Powerline Frequency EMF - NIH
Heating Pad Fires – CPSC
International Advisory Committee for the WHO EMF Project
Review of Technology Transfer Program Grants – NIST
Skin Diseases Interagency Coordinating Committee
OST/CDC ACTIVITIES
Review Consultant for MMWR Articles on Medical Devices
    Review and coordination of revision of the CDC Condom Brochure
    Public Health Laboratory Information System (PHLIS)
Dynamic Light Scattering – NASA & USUHS
Wireless Medical Telemetry TG – AHA

Table 6 – Ad Hoc Postmarket Surveillance Activities

Steris/Olympus Endoscope Sterilization
Oxygen Regulator Fires
Wheelchair Fires
Vascor Pacing Leads
Phacoemulsification
Pall Leukocyte Reduction Filter
Hemostasis Devices
Electrosurgical Units
Interference of Rate Adaptive Pacemakers
Dialyzer Aging/Degradation
Endoscope Washer/disinfectors
Contaminated Dura Mater
Holmium Yag Laser – Lithotripsy – Cyanide

STAMP Program
- Liposuction Devices
- Pacing Leads
- Neurological Shunts

Other consultations
- Telectronics "J" Lead
- Glass Capillary Tubes

Alaris Medical Infusion Pump
Exposure to Ionizing Radiation
EMI of Wheelchairs, cardiac pacemakers & ICDs
Baxter Colleague Infusion Pump
Pulse Oximeter Failure
Bioelectric Impedance Device
Hospital Bed Workshop
Genzyme CABG Retractor Breakage
Silicone in syringes
Vena Cava Filter fracture
Phthlates in IV tubing and bags
FDA/CDRH Emergency Operations Working Group
Medex Trilogy Infusion Pump
Latex Gloves

FORENSIC ANALYSES

Failure of a medical device in-service is seldom without significant adverse consequences to the patient on whom the device is being used at the time. Analyzing the failures and identifying the siblings of the failed device often require understanding the possible mechanisms of failure and deciding on an experimental approach while working with very little data. **Table 7** is an example of the forensic analyses performed this year. OST also provides several calibration services in direct support of CDRH, ORA, and state inspectors of radiation-emitting products. **Table 8** is a list of those calibration services and the numbers of devices from all calibrated sources.

Table 7 – Forensic Analyses

Laser Pointers (10 samples)
Laser Rangefinder (2 samples)
Contamination of hemodialysis machine blood lines
Sunlamps
Ferris Wound Dressings

Table 8 - Instrument Calibrations

Diagnostic X-ray Probes – 1350
Mammography X-ray Probes – 278
KVp Meter - 136
Digaphots - 108
Microwave Probes - 25
Laser Probes – 22
Beam splitter - 1
C-series Calorimeter - 2

RESEARCH

BIOEFFECTS

Cellulose Acetate

Key words: neutrophils, cellulose acetate, hemodialysis, oxidative response, biocompatibility

Following an adverse clinical event involving seven patients undergoing renal dialysis using 12-year-old cellulose acetate hemodialyzers, this *in vitro* study was proposed in an effort to characterize the inflammatory response to the constituent cellulose acetate (CA) fiber materials. Chemiluminescence (CL) and apoptosis assays were used to determine if human neutrophils were activated by cellulose acetate fiber materials and/or are sensitive to degradation/alteration of these fibers over time. For the CL assays, 60-minute exposure was followed by secondary stimulation with n-formyl-met-leu-phe or phorbol-12-myristate-13-acetate. The inflammatory response as measured by the respiratory burst of neutrophils was stimulated ($p \leq 0.05$) by CA fiber exposure significantly over control. There was a trend toward an increased response with exposure to older fibers. Apoptosis was increased 12% with exposure to the more aged fibers versus 2% with the new fibers.

More work is needed to determine the specific nature of the interaction of inflammatory cells with CA materials, but early evidence does suggest that neutrophils are activated by CA and display an altered response to more aged fibers.

Developing a PCR-PNA-ELISA Procedure for Rapid Detection of Point Mutations in *Mycobacterium Tuberculosis* Genes Associated with Drug Resistance

Key words: polymerase chain reaction, PCR, peptide nucleic acid, PNA, in vitro diagnostics, Mycobacterium tuberculosis.

Tuberculosis remains a global health problem, and the emergence of antibiotic drug resistant strains of *Mycobacterium tuberculosis* (MTB), the causative agent of tuberculosis, threatens public health. Recent molecular biological studies have shown that many of the specific genetic mutations that cause resistance in MTB are single-base change ("point") mutations. Classical techniques for detecting drug-resistant mutant strains of MTB are slow and tedious. New methods for quick diagnosis of drug-resistant MTB strains are needed. An OST molecular biologist and collaborators from FDA's Center for Biologics Evaluation and Research (CBER), are developing a PCR (polymerase chain reaction)–PNA (peptide nucleic acid)–ELISA (enzyme-linked immunosorbent assay) procedure for rapid and convenient detection and identification of single-base change ("point") mutations in drug-resistant genes of MTB.

A model system has been developed for this work, and it involves the MTB katG gene, which is associated with resistance to the commonly used MTB antibiotic "isoniazid." The katG gene was cloned by the CBER collaborators into a plasmid vector using techniques of recombinant DNA. The PCR method with fluorescein-labeled primers is used to amplify specific regions of the cloned mutant katG gene. Short biotinylated PNAs that attach to avidin-precoated ELISA plates are then synthesized and used as probes for detecting mutant katG gene DNA sequences. PNA molecules are chemical strands that contain DNA bases attached to a protein-like (peptide) structural "backbone," and they hybridize, or bind, with single-stranded DNA molecules. PNAs are useful probes for detecting mutant nucleic acids because they have high thermal stability, strong binding capacity, and high binding specificity. The PNA probes used in this study are designed so that they will hybridize specifically with DNA sequences of the (denatured) PCR-amplified mutant katG gene (but not DNA sequences of the wild-type katG gene or any non-specific mutant gene). Non-specific DNA sequences are dehybridized by washing at 50-55oC. PNA molecules are chemical strands that contain DNA bases attached to a protein-like (peptide) structural "backbone." PNA probes are useful for detecting mutant nucleic acids because they have high thermal stability, strong binding capacity, and high binding specificity. After hybridization, color is developed following addition of an anti-fluorescein conjugate and appropriate substrate (ELISA procedure), and the amount of color formation is quantified using a spectrophotometer.

Thus far, the hybridization and other experimental conditions suitable for the successful detection (within 24 hours) of mutations in two different positions of the katG gene have been established using 15-mer PNA probes. The detection of further mutations in the katG gene will be investigated by the FDA investigators, and similar studies using an additional

model drug-resistant MTB gene are planned. In addition to development of this in vitro diagnostic procedure, the laboratory experience gained from the project should also enable the investigators to make informed premarket evaluations of commercial in vitro diagnostic devices used for the detection of wild-type and mutant strains of MTB.

Effects of Implant Coatings on Heart Cell Function

Key words: cardiac, biocompatibility, surface modification, calcium, implant

Chemical surface modification techniques are being applied to implant materials to achieve better biocompatibility and permit functional interaction between implant and tissue. Modified surfaces are being testing in a number of cardiac devices, including implant fabrics, heart valves, artificial blood vessels, and pacemaker electrodes. One type of surface modification that has gained recent prevalence is the use of self-assembled monolayers (SAMs) of biocompatible molecules. In anticipation of the use of such surface modification for cardiac devices, scientists in OST have collaborated with the chemistry department at the George Washington University to test the effects of various SAM coatings on heart cell function.

Dissociated cells from chicken embryo hearts were plated onto two different modified surfaces. One SAM was a hydrophilic triamine; the other was a hydrophobic perfluorinated compound. Both anatomical and functional characteristics of individual heart cells were measured on each of these surfaces. Quantitative morphology showed no significant differences in either the size or shape of the cells. Intracellular electrical recording demonstrated normal electrical activity of the cells on both surfaces. Optical measurements of intracellular calcium changes during the cardiac action potential showed abnormal calcium signals from cells grown on the perfluorinated surfaces. The calcium signal in these cells was smaller and had a missing component. Calcium in heart cells is related to contractility, cellular regulation and signaling. The abnormal calcium changes of cells grown on this surface would imply functional impairment. The fact that important functional differences were demonstrated with no significant difference in morphology underscores the need for physiological testing of medical device materials.

Safe Use of Electrostimulators in Acupuncture

Key words: electroacupuncture, stimulator calibration standards

OST has been involved with issues of infection control regarding acupuncture needles; however, the next issue to be confronted by CDRH with medical devices associated with acupuncture will be electrostimulators. The concern with these devices is whether they have the potential to do serious harm through electric shock or excessive current. An electrical engineering mentorship student from Marquette University performed an analysis of representative devices used for electroacupuncture, specifically the electrostimulators used in conjunction with inserted acupuncture needles. The approach consisted of comparing the claimed outputs of a number of marketed electrostimulators with electronic evaluations (via oscilloscope) and combining that information with actual use parameters obtained from electroacupuncture clinical trial publications, as well as

with safety considerations provided in performance standards (ASTM) and FDA safety concerns. The measurements indicated that the output from each of the representative stimulators was significantly different from the manufacturer's values. Thus, each stimulator should be individually calibrated. Determinations of the unbalanced current resulting from the pulse waveforms indicated that at high pulse frequencies (100 Hz) there may be localized injury from the excess current. Thus, the users should be adequately trained to minimize risk from using the electrostimulators in the clinical setting.

Safety of High Frequency Electrical Stimulation of the Nervous System

Key words: excitotoxicity, nerve, deep brain stimulation, spinal cord, cochlea, stimulation

Electrical stimulation is used to treat a number of nervous system disorders as well as in the replacement of damaged neural elements. Treatments generally involve stimulating nerves at a rate no higher than the maximum impulse rate of nerve cells, typically 300 pulses per second. Recent clinical evidence, however, suggests that high-frequency stimulation may increase the therapeutic value of nerve stimulation devices. Examples include the improved relief of pain via spinal cord stimulation, better sound with cochlear implants, and the treatment of Parkinson's disease symptoms with deep brain stimulation. However, the safety of these forms of high-frequency electrical stimulation has not been systematically investigated. OST scientists are performing neurophysiological experiments combined with theoretical analyses designed to determine the deleterious effects of high-frequency electrical stimulation on neural tissue.

Theory predicts that high-frequency current pulses will depolarize nerve cells, lower the threshold of stimulation, and increase excitability. These occur with an increase in sodium ion permeability. OST experiments involving intracellular microelectrode recording from single-nerve cells demonstrated that depolarization does, in fact, occur. These experiments also show that high-frequency stimulation increases excitability and relieves action potential conduction block. The resulting safety concern is that prolonged stimulation will cause an ion imbalance due to intracellular sodium or calcium ion accumulation. This imbalance could overload the metabolic machinery of the nerve cell and cause a toxic effect (excitotoxicity). Preliminary experimental evidence has demonstrated that short periods of high frequency stimulation cause the activation of a metabolic pump for extruding sodium ions from cells. This metabolic pump activation causes an eventual depression in excitability. Future studies will investigate the safety relevance of the excitability changes and the conditions under which neural damage could occur from high-frequency stimulation.

Laboratory Testing of Radiofrequency Cardiac Ablation Devices

Key words: cardiac, ablation, arrhythmias, radiofrequency, RF, thrombus

Radiofrequency (RF) catheter ablation is a commonly used procedure for the management of cardiac arrhythmias. The procedure uses RF electrical energy delivered via catheter electrode(s) to generate thermal lesions, which disrupt the aberrant electrical pathways that cause potentially lethal cardiac arrhythmias. One of the difficulties in researching the

heat-transfer mechanisms is that much of the available data regarding heat-transfer issues have been conducted in animal studies. The variances in the numbers from study to study make the interpretation of mechanism difficult to determine. Several courses of study have, therefore, been undertaken in the past year to address this issue and include 1) development of durable simulated human tissue materials (phantoms), and 2) development of an advanced convective heat transfer test cell.

A significant effort has been applied towards the development of phantom materials over the past several decades. The majority of this work has been directed towards microwave and ultrasound applications. Nearly all phantom materials used at ablation frequencies (480-550 kHz) are water-based salt solutions, since the mode of heating is primarily resistive heating. These materials are effective in evaluating electric field strength and thermal fields in homogeneous systems. However, these methods are not effective in evaluating heterogeneous systems that involve materials that have several different electrical properties. One technique for examining these heterogeneous systems is to use a bi-phasic system where a liquid and a solid each represent different materials (e.g. blood and heart muscle). However, because both materials are typically water-based, ion exchange occurs between the materials and each material is degraded significantly after only a few minutes. OST scientists have developed several new phantom materials that are not salt-based and are not, therefore, susceptible to this ion exchange. Used in conjunction with existing phantom materials, these materials will extend the ability to examine more complex systems.

Researchers also directed their efforts during FY 1999 toward developing a heat transfer test cell to examine heat dissipation issues, both at the surface of a phantom and in the near electric field of an ablation electrode. A sophisticated test cell containing these phantom materials has been developed that produces a series of holographic projections of the thermal washout from ablation electrodes exposed to a flow field. The goal of this effort is to refine understanding of heat transfer phenomena where significant blood flow is involved in order to evaluate the potential for adverse effects downstream from the ablation site.

In-Vitro Safety Studies of Cardiac Electrical Defibrillation Devices

Key words: cardiac, stimulator, defibrillator, dysfunction, safety

OST performs safety studies on medical devices for electrical defibrillation of the heart. This work applies to a number of devices, including implanted and external cardiac defibrillators. The work concentrates on the possible deleterious effects of these devices on live cells and how these harmful effects can be avoided. In FY 1999, OST scientists continued their work on the safety of electroshock from cardiac defibrillators and focused on the mechanism by which strong electric shocks can induce cardiac dysfunction.

Both automatic implanted cardioverter defibrillators (ICD) and the recent pediatric use of automatic external defibrillators (AED) can generate local electric fields in the heart that are capable of inducing cellular dysfunction. Previous OST studies have demonstrated that electroshock-induced dysfunction involves a prolonged calcium ion elevation in heart

cells. The calcium elevation is associated with a period of refractoriness to pacing. Such cellular dysfunction is related to the production of secondary arrhythmias following defibrillator shocks. For this calcium-related dysfunction, OST scientists determined its threshold, relationship to shock strength, relationship to shock waveform, and the cell locale of the effect. A drug that blocks the calcium channel blocked much of the calcium increase following a strong shock but not the refractoriness to pacing.

Experiments performed on heart cells with different channel characteristics showed that the calcium elevation is due to contributions through nonspecific membrane pores, through calcium channels, and from cytosolic stores. Strong shocks are hypothesized to cause an initial poration of the cell membrane, entry of sodium of calcium ions, cell depolarization, opening of voltage-sensitive calcium channels and the release of cytosolic calcium stores. This hypothesis suggests how drugs and metabolic state can modulate defibrillator safety and effectiveness.

Production of Autoantibodies in Response to Silicone Gel/Oil

Key words: autoantibodies, silicone gel

Studies have been conducted using a female rat model to assess the production of autoantibodies in response to the injection of silicone gel/oil (taken from a breast implant) mixed with connective tissue proteins. Results of this study demonstrated the presence of anti-collagen antibodies in the serum of rats injected with only oil or only gel/oil. To confirm the results of these studies, the 21-month experiments are being repeated using normal Sprague-Dawley rats and autoimmune susceptible Dark Agouti rats. In addition to the test emulsions used in the initial experiment, scientists included oil and gel from a second source.

Large Animal Cardiovascular Research Program

Key words: cardiovascular, animal models, biomechanics, interventional radiology

CDRH has established a large animal cardiovascular research program to develop and study models of cardiovascular disease, vascular injury, and long-term vascular implant performance. This research brings together an interdisciplinary group of both government and non-government scientists and clinicians with expertise in cardiovascular physiology and pharmacology; radiology; pathology; cardiology; animal science (swine); tissue biomechanics; and the molecular biology of vascular disease. The laboratory, which is located at the FDA's Center for Veterinary Medicine in Laurel, Maryland, can be used for animals ranging from rodents to large swine. The space includes a small animal procedural lab, wet lab, gross pathology lab, in vitro physiology lab, pre- and postoperative holding areas, and an interventional radiology/surgery suite with a supporting darkroom and film processor. The interventional radiology suite allows performance of diagnostic angiography as well as interventional procedures (e.g., balloon angioplasty, stent placement, and selective catheterization) under sterile conditions with general anesthesia. The laboratory also utilizes the long-term holding facilities of the FDA/CVM complex at Greenbelt, Maryland.

OST scientists in collaboration with ODE are using the laboratory to study the effects of gender and hormonal state on the function and mechanical properties of coronary arteries and on the healing response of arteries to balloon injury. The motivation for the study is the observed greater incidence of cardiovascular death in postmenopausal women and in men of all ages compared to premenopausal women. There is epidemiological evidence that estrogen replacement therapy in postmenopausal women provides some protection against coronary artery disease. The proliferative response of an artery following angioplasty, a major cause of restenosis following this treatment, may also be reduced by estrogen therapy.

In this study, the effects of balloon injury of the coronary artery are evaluated in a swine model representing permutations of gender and hormonal state. The four cohorts are normal controls (mature and hormonally intact males and females), castrated males, and ovariectomized females (a model of female menopause) with and without estrogen replacement. The left anterior descending coronary artery is intentionally injured by balloon dilation, the same technique used in the treatment of coronary artery disease. This results in a proliferative healing response by the vessel wall. One month later, the heart and coronary arteries are surgically isolated, and coronary blood flow is directly measured and evaluated for changes in response to directly infusing vasoactive drugs directly into the coronary artery. Samples of the coronary artery are collected for in vitro measurement of biomechanical and biomolecular properties and smooth muscle contractility. Researchers then perform a complete histopathological study of the injured site. The scientists also collect samples to study differences in gene expression relevant to normal and abnormal function of the vascular wall.

The project addresses gender and hormonal influences on hemodynamic, biomechanical, pathological, and molecular parameters of normal vascular function as well as the responses of the vasculature to injury. The results should shed light on gender and hormonal differences in the progression and treatment of cardiovascular disease in humans and allow for better definition of the preclinical (animal) testing which should be conducted prior to testing cardiovascular devices in humans.

BIOEFFECTS-RADIATION

Quantitative, Biologically Relevant Parameters for Testing and Standardizing Skin Response to UV

Key words: UV sensitivity, ultraviolet radiation, sunlamps

FDA regulates a variety of ultraviolet radiation (UV)-emitting or –transmitting products including sunlamps, sunscreens, cosmetics, and photosensitizing drugs. The number of people who use such products is very high.

Acute and delayed adverse effects of exposure to ultraviolet radiation (UV) are widely recognized. To improve public health policies in this area, FDA is actively involved in revising or developing national and international standards (e.g., the FDA Sunlamp Performance Standard; IEC 60 335-2-27, UV and IR Appliances; UL 482, Sun/Heat Lamps; CIE TC6-48, Typical Minimal Erythema Doses. Also, FDA currently develops or revises guidelines for different UV-related products. However, the current knowledge provides inadequate scientific basis for such standards, guidelines, and policies. This applies to all users of the UV-related products. The gaps in our knowledge are particularly severe for non-Caucasians. In fact, it is not clear how to test or predict human UV responses and general UV sensitivity.

For these reasons, the Human Photosciences Research Facility has been established at CDRH. It includes a UV exposure room, a biopsy room, a biopsy processing lab, photographic documentation studio, a measurement section housing three optical instruments (Minolta spectrophotometer, DiaStron Erythema/Melanin Meter, and an Optical Coherence Tomograph obtained from Philips Research, The Netherlands). Also included are two mechanical instruments (BTC-2000 Suction Device and Diastron torsional ballistometer), high-frequency ultrasound (Taberna Pro Medicum DUB-20 Plus) equipment, and a reception/conference room. This facility is used by a multidisciplinary team, including investigators from OST and OSB as well as those from CFSAN, NCI/NIH, Washington Hospital Center, and Philips Research Laboratories. The team investigates the usefulness of novel physical parameters and biomarkers for testing and standardizing human skin response to UV. This study is conducted on 110 volunteers divided into 11 groups on the basis of their skin type (Fitzpatrick, I-VI) and their racial/ethnic origin (OMB classification 0990-0208: American Indian or Alaska Native; Black or African American; Asian; Hispanic or Latino; Native Hawaiian or Other Pacific Islander; White.) Small (2x2 cm) areas are exposed to different UV doses. Then, at different times, the erythema (skin reddening), pigmentation (tan) and edema are evaluated by eye and using several instruments. Epidermal elasticity and viscoelasticity are measured. Structural changes are examined using optical coherence tomography and the ultrasound technique. Skin biopsies from the exposed and unexposed areas are collected and analyzed for cellular and molecular changes.

It is critical to the outcome of this study that the optical radiation dosimetry be of the utmost integrity (e.g., traceable to NIST). Accurate spectral measurements of UV radiation are required, not only to determine the exact exposure schedule for each individual - which varies with presumed skin type - but also to protect ancillary personnel from inadvertent exposure to UV.

Figure 1 shows the emission spectrum of the exposure source used in the CDRH human study. External filtration (Kodacel cellulose acetate film) is required to remove wavelengths neither found in natural sunlight or used in tanning devices.

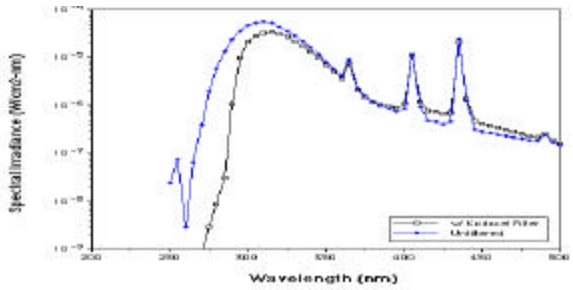


Figure 1. FS Lamps – with and without filtration

As mentioned above, this study afforded OST scientists the opportunity to use and evaluate an Optical Coherence Tomograph (OCT) (from Philips Research Laboratories). It was hoped that this device might be useful in determining the structure of the upper layers of the skin and aid in predicting skin UV sensitivity by revealing UVB-related effects not measurable by other means. The device employs a 670-nm wavelength laser diode to interrogate the top 1 mm of skin surface. OST scientists used the image data to examine the optical attenuation of UV-exposed and unexposed skin. Early results indicate that a correlation exists between the attenuation of 670-nm photons through the top 0.6-0.8 mm of *unexposed* skin and the experimentally determined MED. Data for eleven subjects (each displayed in a different color) are shown in **Figure 2**.

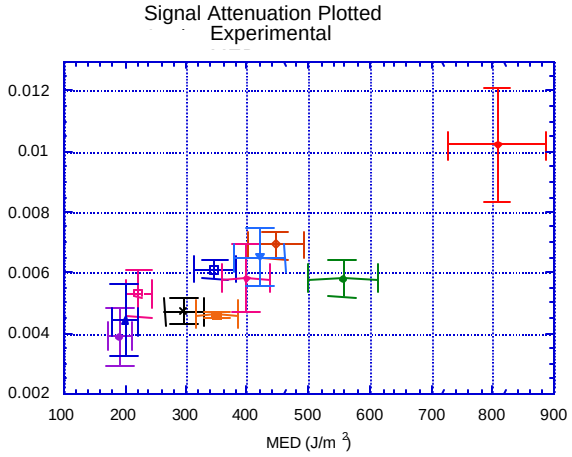


Figure 2. Signal attenuation (average ± standard deviation) vs. MED (± 10% instrument measurement error)

The study is ongoing at this time, and the data have been collected on 38 subjects. The results confirm substantial variation of Minimal Erythema Doses (MED) within conventional skin type categories. The data indicate that racial/ethnic origin is not a primary factor determining individual UV sensitivity. They also confirm induction of extensive DNA damage following exposure to 1 MED.

The results of this study will facilitate safety and efficacy analyses of many FDA-regulated products and should help to select parameters for clinical trials of FDA-

regulated products. They should provide support for modernizing public health policies in the area and help consumers to protect themselves from skin cancers and premature skin aging.

Full Spectrum Apoptosis

Key words: apoptosis, cell death, apoptotic pathway, megapore

Many wavelengths of radiation cause apoptosis. Apoptosis, or Sunburn Cell, is a term that only describes the morphological changes a cell undergoes during this mode of cytotoxic cell death. The terms immediate, intermediate, and delayed apoptosis segregate the different apoptotic mechanisms into three kinetic categories, while the terms pre-programmed cell death (prePCD) and programmed cell death (PCD) describe the underlying mechanisms. Immediate apoptosis (T≤15 min post exposure) triggered by photodynamic therapy (PDT) or UVA1 singlet-oxygen damage to mitochondrial membranes depolarizes the inner transmembrane potential, which opens the mitochondrial megapore at the "S" site (sulfhydryl sensitive). It is a prePCD mechanism of apoptosis because all the necessary components are constitutively synthesized and only need to be activated and/or released. Intermediate apoptosis (T>15 min≤4h) initiated by PDT, UVA, high-dose UVB or UVC damage to receptors and/or cytoplasmic components leads to opening the megapore at the "P" site (pyrimidine dinucleotide sensitive). It is also a prePCD mechanism. Delayed apoptosis (T>4h) induced by PDT, UVA, PUVA, UVB, UVC and X-ray damages to DNA also eventually leads to opening the megapore at the P site. However, it is a PCD mechanism of apoptosis because transcription and/or translation are required. Each mechanism activates one of two final apoptotic pathways. PDT and UVA can trigger immediate apoptosis by causing the cyclosporin A-sensitive S site of the megapore to release apoptosis-initiating factor, which activates a final apoptotic pathway that is primarily caspase-independent. Whereas, PDT, UVA, PUVA, UVB, UVC, and X-rays initiate intermediate and/or induce delayed apoptosis by causing the cyclosporin A-insensitive P site of the megapore to release cytochrome c, which activates another final apoptotic pathway that is primarily caspase-dependent. The apoptotic mechanism(s) which is (are) initiated depend(s) somewhat on the cell type; but primarily depends on the wavelength and dose of radiation, as well as the type, concentration, and intracellular location of the photosensitizer or chromophore.

UVA1 Radiation Triggers Two Different Final Apoptotic Pathways

Key words: apoptosis, cyclosporin A, pre-programmed cell death, mitochondria, radiation

Because UVA1 radiation is used therapeutically, this in vitro study addressed the question, "how does it work?" To begin addressing this question, UVA1 radiation was first established to reduce the survival of transformed T and B lymphocytes in a linear, dose-dependent manner using clonogenic assays, transmission electron microscopy, Annexin V, and flow cytometry. The primary mechanism was determined to be immediate (<20 min) preprogrammed cell death (pre-PCD), an apoptotic mechanism that does not require protein synthesis post insult, by quantifying the apoptotic cells over time in the absence or presence of a translation inhibitor.

To explore how UVA1 radiation triggers immediate pre-PCD apoptosis, reactive oxygen species (ROS) and mitochondrial function were altered during exposure using a variety of agents, while a specific fluorescent probe, JC-1 (5,5', 6,6'-tetrachloro-1,1',3,3'-tetraethylbenzimidazolcarbocyanine iodide), was used to examine mitochondrial transmembrane depolarization. To show which UVA1-mediated ROS damages mitochondrial membranes, the following established ROS generating systems were used: 1) singlet oxygen, rose bengal or delta-aminolevulinic acid (increases endogenous protoporphyrin IX) with visible light; 2) superoxide anions, vitamin K_3; 3) hydroxyl radicals, X-rays; 4) mixed ROS, high-dose UVB; and 5) none, anti-Fas cross-linking antibody and blocking antibody. Cyclosporin A was used along with these systems to distinguish between the two final pathways because it inhibits mitochondrial permeability transition (PT) or megapore opening at the "S" site (sulfhydryl sensitive) but not at the "P" site (pyrimidine dinucleotide sensitive).

The collective results show UVA1 radiation triggers both final apoptotic pathways. It primarily mediates singlet-oxygen damage to the cyclosporin A-sensitive S site of the mitochondrial megapore, triggering immediate pre-PCD apoptosis by depolarizing the inner transmembrane potential causing PT. However, it also mediates superoxide-anion damage to the cyclosporin A-insensitive P site of the megapore. The S site releases apoptosis-initiating factor, which primarily triggers a caspase-independent final apoptotic pathway, while the P site releases cytochrome c, which primarily activates a caspase-dependent final apoptotic pathway.

Potential Therapeutic Uses of Magnetic Fields to Mitigate Reperfusion Injury

Key words: magnetic fields, coronary reperfusion injury, ischemic stress

Continuing from previous investigations on the potential adverse effects of magnetic fields, OST investigated one of several proposed therapeutic effects of magnetic fields. Following a myocardial infarction, perfusion of the myocardium may be re-established by therapeutic interventions including thrombolytic agents and/or percutaneous angioplasty. Reperfusion of the hypoxic myocardium results in the formation of reactive oxygen intermediates which have deleterious effects, including further necrosis of cardiac tissue. Other investigators have reported that applying weak magnetic fields to avian embryos prior to re-perfusion prevents the toxic effects of re-oxygenation in this model. It has been postulated that this protective effect is due to the activation of heat shock factors by magnetic field exposure. These investigators believe that this avian model suggests the possible therapeutic use of weak alternating magnetic fields prior to thrombolytic therapy or angioplasty in patients being treated for myocardial infarction. Since the study was funded by commercial interests and a patent has been awarded for a medical device based on the reported effects, it seems likely that an IDE will be submitted to CDRH for human studies.

In order to position the Center to evaluate submissions involving this use of magnetic fields to treat coronary artery disease, OST attempted to verify the investigations reported in the avian embryo. Chicken embryos were exposed by "windowing" the eggs and the

embryos made anoxic using an argon atmosphere. Embryos pre-exposed to 60-Hz 8 μT magnetic fields for 20 minutes were compared to unexposed control embryos. Observers blinded to the treatment scored the embryos at 30-minute intervals checking for the presence or absence of heartbeat. When the percentage of surviving control embryos had fallen to 30-50%, the embryos were re-oxygenated, and myocardial toxicity was monitored by observing the return of a heartbeat. Experiments using a total of 182 control embryos and 169 magnetic field exposed embryos showed a slight trend toward higher recovery in exposed embryos (70% vs. 65%), but the difference was not statistically significant. OST concludes that it is unlikely that weak magnetic field exposure protects myocardium against reperfusion injury and that any proposed clinical trials of this treatment be supported by data from a mammalian model.

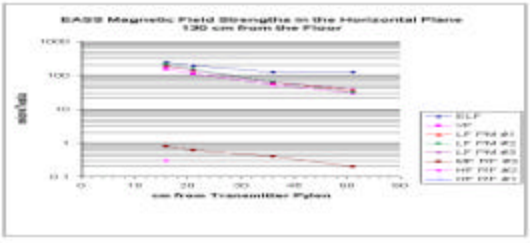
ELECTROMAGNETIC INTERFERENCE

Electronic Article Surveillance Systems (EASS) and Metal Detectors as Sources of Interference with Implanted Medical Devices

Key words: magnetic field, electronic article surveillance systems, EASS, electromagnetic interference, implanted devices, metal detectors

OST engineers have completed magnetic and electric field mapping of eight electronic article surveillance systems (EASS). The results of these tests were published in the September-October issue of Compliance Engineering. These data were also presented at the 1999 annual Association for the Advancement of Medical Instrumentation (AAMI) symposium. **Table 9** and **figure 3** provide summaries of these electromagnetic field-strength measurement data. A discussion of the EASS issue was presented at a public meeting of the CDRH Technical Electronic Product Safety Standards Committee (TEPRSSC) in conjunction with a review of the risks associated with exposures to magnetic fields of patients wearing certain medical devices. These risks included interference with the proper operation of implanted medical devices, such as cardiac pacemakers and defibrillators, and spinal cord stimulators. Comparisons of the electromagnetic field measurements made in the laboratory with performance requirements with the European Standard EN 50061/A1 -1995 (Safety of Implantable Cardiac Pacemakers) are shown in **figure 4.**

Figure 3. Summary of electromagnetic field strength data



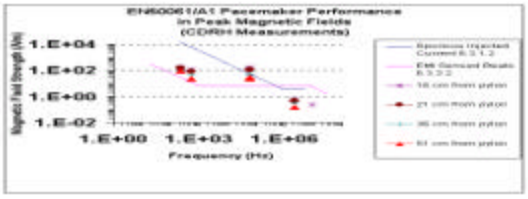


Figure 4. Comparison of electromagnetic field measurements in laboratory using European Standard EN 5006/A1-1995

A walk-through metal detector was obtained from the Federal Aviation Administration for use in the medical device interference study. OST's three-dimensional electromagnetic field-strength mapping apparatus was relocated to a new laboratory. The optimal location space was identified via comparative measurements in the laboratory location vs. measurements in the OST/EPB outdoor test facility (**figure 5**). The required support structure was designed and constructed using non-magnetic components.

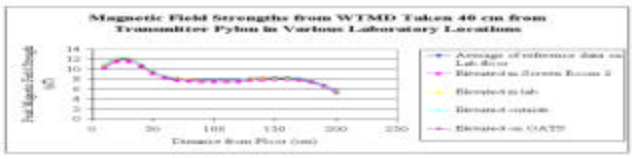


Figure 5. Magnetic field strengths taken 40 cm from transmitter pylon

EAS System	Frequency	Modulation	Magnetic Field Strength (μT)*	Pylon Separation (cm)
Magnetic #1 (ELF)	219 Hz	CW	122	81.3
Magnetic #2 (VF)	535.7 Hz	CW	72	73.7
Pulsed Magnetic #1 (LF)	58 kHz	Pulsed - 10% duty cycle 1.66 ms ON 16.6 ms period	64.9	182.9
Pulsed Magnetic #2 (LF)	58 kHz	Pulsed - 10% duty cycle 1.66 ms ON 16.6 ms period	62.2	182.9
Pulsed Magnetic #3 (LF)	58 kHz	Pulsed - 10% duty cycle 1.66 ms ON 16.6 ms period	61.7	274.3
Swept RF #1 (HF)	7.2-9 MHz	FM - 12 ms/sweep	<1.0	91.4
Swept RF #2 (HF)	7.6-8.9 MHz	FM - 12 ms/sweep	<1.0	91.4
Swept RF #3 (MF)	1.8-2.1 MHz	FM - 4.2 ms/sweep	1.0	182.9

Table 9. Maximum Magnetic field Strengths of Eight Electronic Article Surveillance Systems (EASS). (* 36 cm from Transmitter Pylon Centered 130 cm from Floor)

IMAGING

Mammography

Key words: mammography, phantom, dosimetry, thermoluminescent dosimetry

Work has continued in the area of mammography on the optimized mammography system (OMS). The film-screen combination used with the system for the past several years consisted of a Kodak Min-R Medium screen and Kodak Min-R H film. Both of these products have been discontinued, so it was necessary to find a suitable replacement with the high sensitivity (speed) required by the OMS. Suggestions were solicited from manufacturers, and Kodak and Fuji responded. The film-screen combinations recommended by both firms were tested with the OMS at the NIH Clinical Center. Both have sufficient sensitivity. A series of phantom images was made with each combination, and scored by the radiologists working on the project. A final choice of the combination to be used for the clinical trial of the OMS will be based on analysis of the phantom scores.

OST continued the project to provide experimental verification of the exposure-to-dose conversion factors used in the American College of Radiology Mammography Accreditation Program. The measurements with the conventional source configuration (Mo-anode tube, Mo filter) were successfully concluded, showing agreement with previous experiments and theoretical calculations that is within the limits of experimental error. The graduate student working on the project received a Master's degree from Georgetown University in April 1999. While this work validates the method used, the work of verifying the conversion factors for new, dose-reducing anode and filter choices remains to be completed.

OST also continued work on the project evaluating the potential for reading the mammographic phantom images by machine. The two packages obtained from outside sources and the OST-developed software were compared quantitatively on a range of phantom images. The results were presented at a Mammography Symposium jointly sponsored by the University of Virginia and the American Association of Physicists in Medicine, and was held in Charlottesville, Virginia, on September 24-25, 1999.

RF Safety of Patients with Metallic Implants in Magnetic Resonance Imaging

Key words: MRI safety, Implants, specific absorption rate, magnetic fields

Magnetic Resonance (MR) imaging has become a widely used medical procedure. Manufacturers of implant medical devices are routinely submitting claims that their devices are safe and effective in an MR environment. As a result, OST scientists have been studying patient heating due to the interaction of metallic implants with the strong radio frequency (RF) magnetic field produced by MR devices.

MR devices produce an RF magnetic field that results in RF energy absorption by patient tissues. The absorbed RF energy, denoted by the parameter Specific Absorption Rate (SAR), usually occurs in non-uniform patterns within the patient's body. A metallic implant can interact with the RF magnetic field of the MR device resulting in further concentration of local RF heating in tissues near the implant.

Computer modeling was performed of the specific absorption rate (SAR) distribution in a realistic model of the human body containing a metallic implant (24-cm long wire). This

model was exposed to circularly polarized fields from a model of an MR birdcage body coil (64 MHz, 1.5 Tesla). The results were compared with those obtained from a human-shaped phantom composed of only muscle tissue and a rectangular (39x25x55 cm) phantom model filled with either muscle tissue or cerebro-spinal fluid (CSF). The results of the calculations indicated rather different patterns of SAR values in the phantom models. These differences in SAR patterns may be caused by several factors, including differences in geometry and dielectric properties between the models.

The heating pattern near the metallic implant concentrates at the tip of the metallic wire. Although different SAR distributions are observed in the realistic human model--the muscle human model and the muscle rectangular model--the heating at the tips of the metallic wires in all three models are evident. However, the RF field penetration into the interior of the saline (CSF fluid) rectangular model is low compared to the rest of the models, resulting in very little heating at the tip of the metallic wire. The result of this study indicates the need to use the proper model and the proper MR coil source to represent the realistic SAR patterns of patients with metallic implants exposed to MR RF magnetic fields.

Virtually all manufacturers of implantable devices that claim MRI compatibility utilize experimental models of the human body with simple, nonrealistic configurations. The OST computer modeling indicates that this can cause an underestimate of the induced SAR and resulting heating caused by implants used in patients undergoing an MRI exam .

Maximizing Velocity Measurements with Digital Particle Image Velocimetry

Key words: flow visualization, DPIV validation model, standard test method

Digital particle image velocimetry (DPIV) is a flow visualization tool that provides a quantitative two-dimensional velocity vector map of flow patterns in clear plastic models. This measuring technique can identify zones of flow stagnation or high shear stress, either of which can lead to adverse effects in blood flow devices, such as artificial heart valves. The previous DPIV flow visualization system utilized a video camera, room lighting, and a dual-pulsed strobe-lighting source to measure velocities up to 1 m/s. Since peak blood velocities in the human aorta and through heart valves can reach several m/s, some improvements and new developments were required.

These improvements included new instrumentation consisting of a digital PIV camera and frame grabber, an acousto-optic laser modulator (AOM), a digital delay/pulse generator, a fiber optic link, and new version of the DPIV software to integrate this new equipment. The digital camera is operated in the triggered dual exposure mode, and the camera and frame grabber are integrated for real-time image capture and storage on a DVD recorder with a new version of Visiflow DPIV software (Ver 6.14). The CW argon laser is modulated by applying a dual-pulse TTL signal to the input of the acousto-optic modulator, which produces a modulated laser beam with a repetition rate of 30 Hz. The characteristics of the driving pulses to the AOM are adjustable and include the pulse width, time between pulses (Δ t), and the duty factor for the pulses (on time/off time).

Scientists measured a dry powder linear and rotary model, along with a Poiseuille fluid flow model. Schematics of the setups for these tests are shown in **figure 6** (linear/rotary motion model) and **figure 7** (Poiseuille fluid flow model). Preliminary results demonstrated correct direction vectors but large velocity magnitude errors for the linear/rotary models as well as for the Poiseuille fluid flow model. This error is attributed to the large duty factor (longer laser pulses) required to properly illuminate the models at the higher velocities. This result is similar to those obtained by others and indicates that high duty factors limit the accuracy in measuring high fluid velocities.

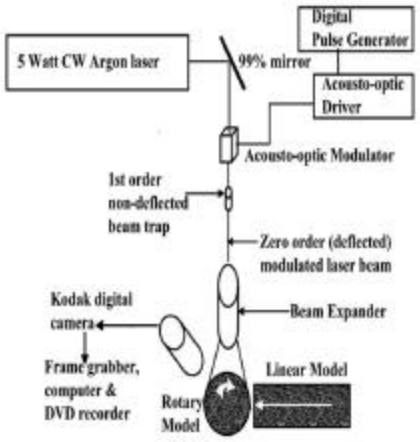


Figure 6. Schematic of dry powder linear/rotary motion model for DPIV validation study

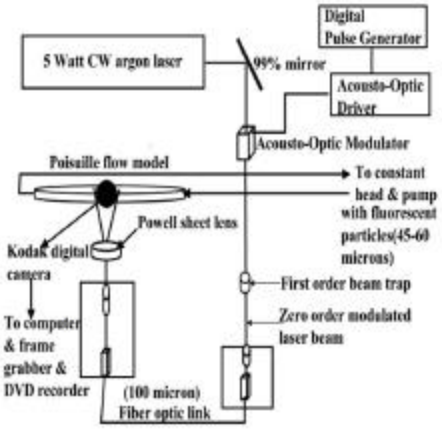


Figure 7. Schematic for Poiseuille fluid flow model for DPIV validation study

OST is currently in the process of characterizing the maximum useful measurable velocities for all three validation models (linear, rotary, and Poiseuille fluid flow) using various combinations of duty factors and time between images. In order for DPIV to accurately measure velocity, the illuminated sequential images must show the particles as particles and not streaks. The longer laser pulses cause this streaking. However, lower duty factors may not provide enough illumination for proper analysis. Possible solutions to this laser power problem will be investigated in FY 2000.

Tissue Characterization

Key words: ultrasound, pattern recognition, liver disease, prostate cancer, research

OST scientists, in collaboration with their colleagues from Georgetown University (GU), George Washington University (GWU), and the University of Vermont (UVM), have begun a study titled “Combining Clinical, Sonographic, and Elastographic Features to Improve the Detection of Prostate Cancer,” supported by funding from the US Army. This 2.5-year effort will apply and evaluate the use of ultrasonic tissue characterization, elastography, and pattern recognition methods that OST scientists and their collaborators have developed to detect prostate cancer. The efforts this year were focused on the

relocation of the data-acquisition portion of the investigation to the UVM laboratory. Ultrasound (US) data are now being acquired from about one to two *in vitro* prostatectomy samples per week; data from about 30 samples have been acquired thus far. There have been advances in the last year in the US data-acquisition process as well as the data-analysis process. OST has also been working with the pathology department at UVM to better align the pathology data with the US data. Additionally, an OST-sponsored doctoral student at GWU defended his dissertation on "Classification Performance and Reproducibility of New Parameters for Quantitative Ultrasound Tissue Characterization."

IMMUNOTOXICOLOGY/TOXICOLOGY

Effects of Particulates on Immunologic Function – In Vitro Methods

Key words: particles, cytokines, wear and degradation, macrophages, standards

Wear and corrosion of implanted medical devices, such as dental and orthopedic prostheses, may produce particles, which may lead to acute and chronic inflammatory responses in the body. In order to evaluate the inflammatory potential of these particles, OST scientists have continued to refine and develop an in vitro assay using a macrophage cell line that has been incorporated into an ASTM standard (F04.16.01: Practices for Testing for Biological Responses to Particles In Vitro). In this assay, murine macrophage cells are exposed to particles or chemicals and then evaluated for cytotoxicity, production of tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6), both inflammatory cytokines, and production of nitric oxide (NO).

In the past, OST scientists have used this assay to study the inflammatory potential of various types of particles, such as polymethylmethacrylate, titanium oxide, hydroxyapatite, silica, diamond, cadmium oxide, and aluminum hydroxide. A recent interest in evaluating polyethylene (PE) particles required developing special techniques to get the PE particles that float on the culture medium surface to be in contact with the macrophages. The method was refined for floating particles by growing the macrophages on glass coverslips and then inverting the coverslip 'cells-side-down' onto the particles. High density PE (HDPE) and ultra high molecular weight PE (UHMWPE) gave differing results. HDPE in the presence of bacterial LPS, a known macrophage activator, had little effect on TNF-alpha production compared to levels induced by HDPE alone, while UHMWPE plus LPS decreased TNF-alpha production from levels induced by UHMWPE alone. HDPE plus LPS tended to increase NO and IL-6 production, while UHMWPE with LPS tended to decrease NO and IL-6 production.

Thus far, these studies using the in vitro macrophage assay have demonstrated that 1) particles generated from different medical device materials can produce specific and unique TNF-alpha, IL-6, and NO responses; 2) some particles stimulate TNF-alpha production and some do not; and 3) some particles enhance, some inhibit, and some have no effect on the induction of TNF-alpha and NO production by murine macrophages in response to LPS added to the particles.

Immunotoxic and Morphologic Effects of Biomaterial Particles In Vivo

Key words: particles, spleen, in vivo, immunotoxicity

Particles from medical devices may be generated in place within tissue surrounding an implant or may be deliberately implanted in humans, and can cause adverse biological responses. OST scientists from several disciplines have collaborated on a long-term project to examine the effect of chemical composition and size of particles on immune system responses in the mouse to medical device associated materials.

Polystyrene (PS), polyethylene (PE) and/or polymethylmethacrylate (PMMA) particles of various diameters were injected into mice and various parameters were assessed at various time intervals post-injection. The parameters examined included distribution of the particles in peritoneal exudate cells, distribution of the particles within the tissues of the mouse, changes in the morphology and weights of internal organs affected by particle deposits, and changes in several immunologic markers. Preliminary studies showed that chemical composition was the major factor that determines the nature of the response. Particle size was less significant, although it was apparent that some particles were too large to be readily phagocytized. Tissue distribution varied depending on the particle; PMMA particles were transported to the spleen, presumably activating immune responses, while the PS particles remained in the tissue comprising the peritoneal cavity and promoted formation of tissue adhesions. The activation of macrophages measured by the release of nitric oxide (NO) was most evident with the large PS particles, which were not readily phagocytized by single cells. Analysis of the proliferative activity of the spleen cells revealed enhancement of the Con A-responsive population and suppression of the LPS-responsive population by some particles.

Further studies are being conducted to evaluate effects on the specific functions of immune cells in relation to cellular and/or antibody responses. This research was presented at the FDA Science Forum in February 2000 and will be presented at the American Association of Immunologists meetings in summer 2000. The results of these in vivo studies will be compared to the results of OST in vitro studies in order to validate in vitro approaches to biocompatibility testing and ultimately reduce the number of animals needed for extensive testing of biomaterials.

Natural Rubber Latex-associated Allergies: Identification and Quantitation of NRL Proteins

Key words: natural rubber latex, allergies, contributing factors, protein measurement

Natural rubber latex (NRL) in medical devices induces a Type 1 allergy, which may be life-threatening in individuals highly sensitized to NRL-containing proteins. Although awareness of allergy to NRL proteins has increased in the last several years, the prevalence of sensitization in health care providers and in the general population is still significant.

OST scientists are undertaking research projects that are focused on identifying the specific NRL proteins that are allergenic, and they are developing appropriate reagents to be used as standards for the protein and/or allergen quantitation tests. The clinical relevance of various in vitro methods for measurement of potentially allergenic proteins has not been established, and the identity of all latex allergens has not been determined yet. The OST studies revealed a) the existence of a number of major allergenic proteins present in various latex products, and b) the specificity of allergenic response for each sensitized individual depends on the type of product and the pattern of exposure. Based on these findings, it became evident that full and complete evaluation of the allergenic potential of finished NRL products will not be possible until all potential allergens are identified. Through the comparison of NRL proteins from various sources, OST scientists concluded that the total protein level might be a reliable indirect measure of the potential allergenicity of NRL products. They developed a protocol for an ELISA-based immunoassay for protein quantitation based on a rabbit antiserum to NRL proteins. The method was compared with other methods that measure total protein (Modified Lowry and HPLC) and a method that measures specific allergens (RAST inhibition assay). The best correlation of the ELISA inhibition assay thus far has been observed with amino acid analysis by HPLC. Further comparisons will be performed with skin testing as a gold standard for evaluation of allergenicity.

OST scientists have also established an animal model of latex allergy by prolonged exposure of Balb/C mice to NRL proteins, and they also developed an assay for NRL-specific mouse IgE antibodies as a measure of the allergenic response. This assay is providing OST scientists the possibility to study mechanisms, kinetics, and dose-response relationships of allergy induction. This model is also being used in collaboration with industry to evaluate the effects of some environmental factors on the development and intensity of sensitization. The preliminary results indicate that bacterial endotoxin and some disinfectants used in hospitals may, depending on the dose, either enhance or suppress development of NRL allergy. Researchers are continuing efforts to evaluate the potential factors contributing to the development of NRL allergy and to continue further developing methods to reliably predict the potential allergenicity of NRL-containing devices.

Molecular Biomarkers for New Methods for Safety Assessment

Key words: stress proteins, heat shock proteins, pre-clinical test method development, bisphenol A, endocrine disruption, estrogen,, uterus, liver

OST scientists are developing, refining, and validating more sensitive and predictive pre-clinical methods for improved safety assessments, standards, and risk assessments. New molecular biomarkers of exposure and toxicity must be carefully validated with traditional assays and standards for use in preclinical safety evaluation and in risk assessment activities. The rationale for assessing molecular biomarkers is that such targets are usually the first responses induced by potentially hazardous materials and chemicals. In order to be effective and useful, a biomarker should be detectable prior to the onset of overt tissue damage. OST scientists are evaluating enhanced expression of “stress” proteins (sometimes called heat shock proteins) as a method that will more reliably predict

potential adverse effects of device materials and other chemicals in two major target systems in the body: the endocrine system and the liver.

CDRH is concerned with the potential for certain medical device materials or other leachable substances used in device manufacture to mimic or interfere with functions of endogenous hormones and disrupt endocrine homeostasis. For example, bisphenol A (Bis-A), a plasticizer found in some medical devices, has the potential to act as a xenoestrogen. OST scientists are collaborating with researchers at the Department of Biology, George Washington University, on characterizing the estrogenic potential of Bis-A and developing the stress protein response as a molecular biomarker of exposure to estrogenic compounds in general using well known estrogens. The utility of the heat shock protein response to reliably predict the endocrine disruption potential of materials and leachates is being evaluated using side-by-side comparisons with the traditional uterotrophic (uterine hypertrophy, i.e., increased tissue wet weight) assay.

In studies using mice, OST scientists have shown that such changes can be detected in a number of stress proteins (specific heat shock proteins) in the mouse uterus in response to the administration of estradiol, a potent model estrogenic compound. Three endpoints - uterine hypertrophy, histology, and heat shock protein expression - were used to examine the estrogenic response of Bis-A. The changes in expression of heat shock proteins were correlated with the estradiol effects on uterine hypertrophy, the standard assay. In a study comparing the protein induction biomarker response in three strains of mice commonly used in safety testing, one strain was not as sensitive to the effects of estradiol. The major conclusions thus far are that heat shock protein induction is a more sensitive indicator of estrogenic effect than is uterine hypertrophy. Results of the estrogen studies were presented at the 1999 and 2000 Annual Meetings of the Society of Toxicology and form the basis of a graduate student thesis at the George Washington University.

OST scientists, in collaboration with researchers from the University of Arizona, Department of Pharmacology and Toxicology, are also studying the stress protein induction response as a biomarker of exposure and toxicity for chemicals that damage the liver. The study involved the administration of cadmium, a well-known hepatotoxic metal that OST scientists use as a positive control compound, to two strains of laboratory rats that are commonly used in safety testing. The results showed that induction of specific stress proteins occurred prior to the detection of standard clinical indicators of liver damage in one of the rat strains. However, the results also demonstrated significant differences between the two rat strains, i.e., the stress protein response was not induced prior to the onset of severe hepatotoxicity in the second rat strain tested. Results of these studies were presented at the 1999 and 2000 Annual Meetings of the Society of Toxicology.

These studies of new biomarkers for substances that interfere with the endocrine system and for hepatotoxic chemicals illustrate the need to fully understand the expression of particular biomarkers in various model systems (species, strains, cell types and tissues). It is also important to understand the genetic differences that may produce varied results,

especially if these new biotechnologies are to be incorporated as surrogates for or adjuncts to traditional standard methods for safety assessment.

INFECTION CONTROL

Decontaminating Particles Exposed to Bacterial Endotoxin

Key words: particles, lipopolysaccharide, nitric oxide, macrophage

Medical device implants that remain contaminated with bacteria or endotoxin after sterilization procedures can produce fever in the patient. In their submissions to FDA, manufacturers must provide evidence that their sterilized implantable devices are at or below a given endotoxin level. Medical device particles that prove to be sterile by some standard methods may still be contaminated with the endotoxin lipopolysaccharide (LPS), which is not destroyed by autoclaving. Thus, in order to detect macrophage responses to medical device particles that are not influenced by endotoxin contamination using the new ASTM standard (F04.16.01 - Practices for Testing for Biological Responses to Particles In Vitro), it is important that the particles to be tested be sterilized and LPS-free (or barely detectable LPS levels). OST scientists discovered that particles intentionally contaminated with small amounts of LPS stimulate the production of nitric oxide by macrophages in vitro. This method of testing for endotoxin contamination may be more sensitive than the standard limulus amebocyte assay (LAL). OST scientists demonstrated that 70% ethanol can inactivate LPS and may constitute an appropriate method to remove LPS from particles that are being tested for inflammatory potential. This work was published in the *Journal of Biomedical Materials Research* 46: 434-437 (1999).

Transmissible Spongiform Encephalopathies (TSE's) and FDA-Regulated Products

Key words: Transmissible Spongiform Encephalopathies (TSEs), product safety, infection control, TSE risks

As a key member of the FDA InterCenter TSE Working Group (FDA TSE WG) and Chair of the CDRH TSE Working Group, the Center Coordinator for Biotechnology continues to demonstrate leadership and consistent and productive outstanding scientific expertise and efforts in Agency initiatives to resolve numerous cross-cutting scientific and regulatory issues regarding TSEs. These TSEs impact FDA-regulated products with broad implications for public health. Significant initiatives of the FDA TSE Working Group taken to protect public health and to alert industry to appropriate safeguards measures have included 1) letters to the industry, 2) recommendations and guidance, and 3) organizing meetings of the FDA TSE Advisory Committee (TSEAC) to allow for public input into proposed Agency actions. These actions will increase confidence that FDA-regulated products are free of potentially infectious material for TSEs.

The September 1999 International Workshop on Clearance of TSE Agents from Blood Products and Implanted Tissues sponsored by FDA's Center for Biologics Evaluation and

Research (CBER) and CDRH was convened to address the needs of scientists and regulators for biological reference standards and for a harmonized approach to evaluating process-validation data for TSEs. The workshop was a follow-up initiative of the June 1998 Joint Institute for Food Safety and Nutrition International Workshop on TSE Risks that identified the need to discuss standardization of clearance methods for TSE agents and of process validation for those methods on an international level. A summary report of the ATSE Clearance Workshop has been prepared for publication in Developments in Biologic Standardization, and the workshop transcripts have been edited for the FDA web site. The report summarizes the current status and agreement on the need for standardized clearance procedures for products and product components. The World Health Organization (WHO) effort on developing biological reference materials for TSEs is a step in that direction, with FDA input being provided by CBER and CDRH members of the FDA TSE WG.

Additionally, the Center Coordinator for Biotechnology has been key in developing the agenda/issues for the semiannual TSEAC meetings which have included, among others, presentation of the Draft Guidance for the Preparation of a Premarket Notification Application for Processed Human Dura Mater (which has been completed and published) and recommendations on material sourcing for FDA-regulated products from sheep in BSE/scrapie countries. Participation in several national and international forums such as the Cambridge Healthtech Institute Conference on TSEs continues to educate and communicate Agency actions on TSEs and FDA products to the greater scientific community.

Lack of Latex Porosity: A Review of Virus Barrier Tests

Key words: latex, porosity, virus barriers

OST scientists have reviewed evidence regarding whether latex films, as found in condoms and medical gloves, are effective barriers to virus passage together with new data from additional tests. The primary focus was to determine whether latex films are porous, as opposed to having occasional manufacture-induced defects. The published and new evidence from studies using viruses are consistent only with the presence of occasional defects and are not consistent with porosity sufficient enough to allow virus passage. However, quality control of manufactured products based on acceptable quality levels using standardized tests does not guarantee that every sample is perfect. The risk of a specific product is related to the defect rate, the use situation, and the disease of interest, in particular, the quantity of virus-carrying fluid that is needed to constitute an “infectious dose.” The possibility of latex film hydration leading to porosity and ultimately to virus passage was also found to be unlikely and not supported by data.

Calculation of Virus Transmission Through Synthetic Barriers Under Realistic Use Conditions

Key words: virus transmission, computational fluid dynamics, barrier evaluation, transport modeling

Scientists often perform tests on the effectiveness of synthetic barriers (gloves, condoms, instrument sheaths, etc.) to virus transmission under conditions that do not reflect actual use. For example, static test conditions are typically employed while, in reality, considerable motion is associated with use of the barrier. In order to extend laboratory results to more realistic conditions, OST has developed a mathematical model for simulating virus transport through synthetic barriers. The model was recently used to estimate the amount of virus that would be transmitted through a defect in a condom during coitus.

Input into the model was the pressure difference across the condom surface, which was previously measured by OST scientists during coital simulations. The pressure waveform was periodic (a period of 2 seconds was used), with a maximum pressure difference across of approximately 60 millimeters of mercury and a minimum of approximately minus-20 millimeters of mercury. Defects of various cross-sectional shapes were considered, from circles to wide ellipses. The rate constants characterizing the interaction force between the virus and latex were obtained from previous calibration experiments if available. Where rate-constant values were not available, upper and lower bounds were used to determine the range of virus transmission rates.

Virus transport under unsteady conditions revealed several interesting differences compared to steady-state transport through a pore. The oscillatory flow through the pore, which included flow from the outside of the condom to inside during part of the cycle, gave rise to better mixing of the virus suspension in the vicinity on the pore and, consequently, more adsorption of the viruses to the inside and outside surfaces of the condom. The amount of free viruses actually transmitted through the pore was consequently reduced relative to the case of a steady driving pressure. Another interesting feature of the transport was that the quantity of viruses transmitted through the pore decreased slightly with each cycle. This presumably arises from the gradual dilution of the virus concentration near the inlet of the pore, due to diffusion of the viruses to the condom interior surface and subsequent adsorption. For small pores with diameters on the order of a micron, the viruses can diffuse a distance equal to the pore diameter in less than a second, while the period associated with the periodic motion is at least a second. Hence diffusion in the direction normal to the pore axis is an important mechanism.

Calculations using a 10-micron diameter circular-cylinder pore in a latex condom revealed a transmission rate of approximately 10 herpes viruses per cycle, assuming a saline suspending fluid and a titer inside the condom of 1 million viruses/ml. For a suspension of HIV, the flux would be on the order of 1 virus per cycle due to the lower titers of HIV. For hepatitis B, the titers can be as high as 10 billion/ml, and the number of viruses transmitted per cycle could be in the thousands.

OST scientists are presently applying the virus-transport model to other realistic-use scenarios, such as a gloved-hand gripping an instrument during a surgical procedure. In this simulation the brief but intense pressure on the barrier surface produces a surge in virus suspension (e.g., HIV suspended in blood) through any tears present in the glove.

Oven-Aged Latex Gloves Do Not Become Porous

Key words: aged latex, barrier integrity, viral barrier

A modification (see above) to ASTM Test Method F1671-97b (Test Method for Resistance of Materials Used in Protective Clothing to Penetration by Blood-Borne Pathogens Using Phi-X174 Bacteriophage Penetration as a Test System) was employed to determine whether accelerated aging (70^{o} C oven) creates porosity or holes in latex glove specimens that permits virus passage. As part of a collaborative study with PATH, Seattle, Washington, oven-aged gloves were provided that had been oven-aged for 0, 7, 10, or 14 days. Three different latex formulations were investigated. Specimens from gloves just out of the box were tested to determine barrier integrity. The results shown in **table 10** indicate that 4 of 56 specimens allowed very low levels of virus passage, equivalent to passage through single laser-drilled holes of diameters less than <1.5 microns. Since two of the four holes occurred in un-aged specimens, there was no evidence that oven aging reduced the barrier effectiveness.

Table 10. Fraction of aged specimens that allowed virus passage.

Glove	Days at 70 ^{o}C			
	0	7	10	14
Powdered	2*/8	0/4	0/4	1*/4
Powder-free	0/4	0/4	0/4	0/4
Chlorinated	0/4	0/4	1*/8	0/4

Reuse of Single-Use Devices

Key words: cleaning, reuse, disinfection, cardiac catheters (balloon and electrophysiology), biopsy forceps

OST scientists have become increasingly involved in the issue of health care facilities reusing disposable devices, particularly since third-party reprocessors are now becoming major players. These devices are not designed by the original equipment manufacturer to be reused; thus information on how to reprocess them and evaluate them for performance characteristics are not provided. Information is needed on the risks to patients associated with reusing single-use devices.

OST scientists have been conducting experiments to optimize cleaning protocols (accepted for publication in early 2000 in the Journal of Biomedical Materials Research) and to determine the properties that make a disposable device capable of being reused or not. There have been claims against third-party reprocessors that devices are difficult to clean and that there is a chance the devices are not sterile. OST scientists are also addressing issues related to the difficulties sterilizing devices that are not clean and sterilizing devices by ethylene oxide gas or plasma gasses if they are not dry. The effects

of the different sterilization techniques on the mechanical properties of materials used for single-use devices are also being investigated.

Single-use disposable devices are being obtained after a single use in clinical settings at Walter Reed Army Medical Center, Washington, DC. The devices are cleaned in OST laboratories and examined for various performance characteristics. In FY 1999, the major devices studied were the percutaneous transluminal coronary angioplasty (PTCA) catheters, electrophysiology catheters (both mapping and ablating), and GI biopsy forceps. The results of this work have been a topic of discussion at various meetings addressing the issues of reuse of single use devices. These devices are cleaned by first soaking in NaOCl bleach, which ensures proper decontamination for safe handling by the investigators and begins the cleaning process. The cleaning continues by soaking the devices in detergent with enzymes followed by a final rinse in water. The devices are then dried as well as possible and taken for examination and performance testing. This information was presented at the FDA Science Symposium in February 2000 and will be presented at the Annual Meeting of the Society for Biomaterials in May 2000.

PTCA catheters are long, delicate devices, and all have a guide wire lumen that is filled with blood that needs to be carefully cleaned. These catheters have a closed-end balloon lumen that has been filled with a radiopaque dye that is difficult to remove. Failure to remove the dye results in the formation of dried crystals that block the balloon and/or the lumen, rendering the device not reusable. This may not be discovered until after the catheter has been inserted into the coronary artery of the next patient. Sterilization of these devices is also problematic since the lumens are difficult to dry. This problem is compounded due to the existence of many manufacturers of PTCA catheters, with many different models. All catheter models possess different behavior characteristics with regard to cleaning and sterilization. The compliance of some balloons is significantly altered by resterilization. In addition, many are coated to make them more slippery and thus easier to insert. Some of these coatings are adversely affected by resterilization. Therefore, some are clearly not reusable, and some perhaps are reusable with careful cleaning and testing.

OST scientists are also evaluating the ability to clean and reuse electrophysiology (EP) mapping catheters that appear to have no lumens and should be easy to clean and reuse. However, on careful inspection, it is apparent that some of the EP catheters are not sealed and patient blood can penetrate. These are impossible to adequately clean and reuse. Similarly, the ablators appear to be robust with no lumens; however, the handle that controls the movement of the catheter tip and contains the electronic connections is not sealed. The cleaning solution penetrates and then drips for a long time afterwards, which may ultimately affect performance and sterilization.

Simulated reuse studies are being conducted on these devices with various procedures involving immersion in blood, repeat cleaning, and repeat sterilization. The effect on different models of devices is different, and cautions are being raised about the effect of sterilization on some performance characteristics.

OST scientists cleaned and examined over 200 GI biopsy surgical forceps. These devices appear robust and easy to clean. Careful examination revealed the existence of open channels that contain patient material. This material must be cleaned with special equipment using positive pressure or vacuum pressure. These devices have been extremely difficult to dry. These devices are undergoing careful studies to simulate reuse and to evaluate methods for validating cleaning protocols.

Another major reuse issue is the repackaging and resterilization of "opened but not used" devices. Sutures still in their inner packs are a major part of this group of reused single-use devices. To address this issue, OST scientists are investigating the effect of repeated ethylene oxide sterilization on the knot strength of synthetic absorbable sutures. The strength of some sutures was not affected by resterilization, while some showed a decrease in strength and others showed an increase in strength. In addition, the seals on some of the inner packages were destroyed during the reprocessing, allowing the absorbable sutures to be subjected to ambient humidity.

Research is continuing on these devices and additional single-use devices that are known candidates for reuse. The results of the research will be used to classify devices based on risk to the patient with reuse and for guidance documents on how to identify and clean all of the lumens as well as the external surface.

Long-Term Survival of Pseudomonas Aureginosa in Diluted Liquid Disinfectants

Key words: disinfectants, bacterial resistance

In previous studies, OST characterized numerous variables that can decrease the effectiveness of disinfectants or affect their toxicity. Furthermore, during these studies OST identified serious limitations of the tests used to evaluate liquid sterilants and disinfectants. Using sensitive methods, OST scientists recently demonstrated that bacterial spores easily survive liquid sterilants under conditions recommended on the product label. The scientists also demonstrated that bacterial spores and vegetative bacteria are more resistant to disinfecting when deposited onto surfaces, even after periods shorter than those required to development of biofilms. To complicate the situation further, the material onto which bacteria are deposited also has a differential effect on the decontamination outcome.

In current studies, OST investigated weather bacteria could survive on diluted disinfectants long enough to develop resistance or tolerance to concentrated commercial disinfectants. Scientists *Pseudmonas aeruginosa* for the study because the *Pseudomonas* species account for a considerable percentage (7-14%) of the pathogens reported in hospital-wide surveillance. The goal of the study was to compare the long-term survival of *P. aeruginosa* on different disinfectants. Researchers studied a variety of commercial disinfectants whose active ingredients included sodium chlorite, hypochlorite, a mixture of peroxyacetic acid and hydrogen peroxide, phenolics, quaternary ammonium salts, and glutaraldehyde either at alkaline or at neutral pH. Together, these commercial products have been recommended for either disinfecting devices used in patients with AIDS,

decontaminating devices and surfaces during epidemics or bacteriological warfare, or as household disinfectants.

Incubation in disinfectants under the conditions that were recommended on the product label produced bacterial damage that inhibited replication and subsequent formation of bacterial colonies for at least 16 hours. Bacterial colonies recovered to numbers comparable to those in untreated controls within a few days of incubation in new media. This bacteriostatic effect of commercial disinfectants may result in overestimating their bactericidal activity during efficacy testing.

Bacteria developed resistance after long-term (up to 100 days) incubation in four out of six commercial disinfectants studied. A comparable increase in bacterial resistance (in six out of eight disinfectants) resulted after short (30 minutes) deposition onto surfaces or repeated short (30 minutes) exposure to disinfectants. This similarity in increased survival to different experimental protocols could be explained if similar or related protective genes are activated by short-term (30 minutes) contact to surfaces, repeated short-term exposure to disinfectants, or by long-term incubation in diluted disinfectants. Tolerance to commercial disinfectants as described in this study could be developed in hospital settings and account for some hospital infections.

Using Fluorescent Microspheres to Evaluate Barrier Integrity

Key words: latex, barrier integrity, virus, microspheres

Fluorescent microspheres of 100-110-nm diameter can pass through more latex condoms than the 27-nm virus ΦX174. This study was conducted by a mentorship student from a science and technology high school who investigated whether there are properties of fluorescent polystyrene microspheres that could be responsible for these disparate results. The results demonstrated that the microspheres adsorb to condom latex as well as highly-adsorptive viruses (and much more than does ΦX174), and free fluorescent dye is not released when the microspheres are in close contact with latex. These findings argue against the properties of microspheres being responsible for the disparate results. However, an increase in the fluorescence of buffer after contact with condom latex was found, in the absence of microspheres. This increase may require extended contact. Thus, this study found an artifact that could be misconstrued as evidence of fluorescent microspheres passing through latex barriers.

Virus Adsorption Varies with Barrier Material and with Latex Formulation

Key words: viruses, latex condoms and gloves, barrier materials, mathematical model

Laboratory evaluation of a medical barrier to passage of a challenge virus requires understanding any interactions the virus may have with the barrier material. For example, if during passage through a hole the virus binds to the material, lack of passage may suggest that there was no hole in the barrier. At the least, the amount of virus passage would underestimate the size of the hole. This conclusion becomes important when laboratory conditions allow adsorption, but real life conditions do not.

A previous study has shown that herpes simplex virus, bacteriophages MS2, ϕ6, and PRD1, but not ϕX174, in physiological saline adsorbed to a particular brand of latex condom (brand A below). This information was used to calibrate and validate a mathematical model of virus transport with pores in a latex membrane. Using PRD1 (0.063 micron) as the model adsorptive virus, the materials used in other condoms and gloves have been investigated in the same calibration apparatus, including other latex formulations. In addition, materials used for track-etch filters were investigated using virus passage through 0.2 micron holes. The results are shown in **table 11**.

Table 11. Adsorption of bacteriophage PRD1 to materials used in condoms, gloves and track-etch filters.

Material and barrier device	PRD1 Adsorption
Latex condoms	
Brand A, with powder	Yes
+ 0.1% Tween 80 in buffer	No
+ 2% fetal calf serum	No
Brand A, powder removed	Yes
Brand B	Yes
Brand C	No
Latex Gloves	
Brand A	Yes
Brand B	No
Brand C	No
Nitrile Gloves	No
Vinyl Gloves	No
Track-etch Filters	
Polycarbonate (PVP-coated)	No
Polyester	Yes

PRD1 adsorption differed from one material to another and was inconsistent with different latex products, occurring with two of three condom brands and one of three glove brands. Clearly, different formulations for producing these latex products resulted in different adsorption properties, although the powder used with brand A was not responsible for adsorption. These results demonstrate that virus adsorption varies from one barrier material to another and that appropriate testing must be done to ascertain whether this phenomenon will produce artifacts in virus tests of the barrier effectiveness of such materials. Further, it was found that the presence of a nonionic surfactant (Tween 80) or serum could prevent even high levels of adsorption.

LASERS

Fibers and Waveguides Used in Minimally Invasive Surgery

Key words: optical fibers and tapers, fiber-connected surgical instruments

During 1999, OST scientists developed a new technique for coupling laser energy to fibers. The technique uses a tapered piece of hollow glass large enough to collect all laser emissions on one end, and tapers to a small injection diameter equal to the diameter of the fiber on the other end **(figure 8)**. Compared to the use of a lens for coupling, the taper is less expensive and provides a homogenized, uniform beam to the fiber while smoothing the natural mode pattern of the laser output.

The hollow glass tapers were used to provide uniform laser energy to measure and compare the performance of several fluorides, germanium and chalcogenide fibers, and several hollow-coated waveguides **(figure 9)**. An Er:YAG laser at a wavelength of 2.94 microns was used to help measure transmission. When compared with hollow waveguides, the tested infrared fibers provided lower attenuation and almost no losses associated with bending radius. Conversely, hollow waveguides have the advantage of broad band transmission, lower cost to fabricate, good strength, and no toxicity problems.

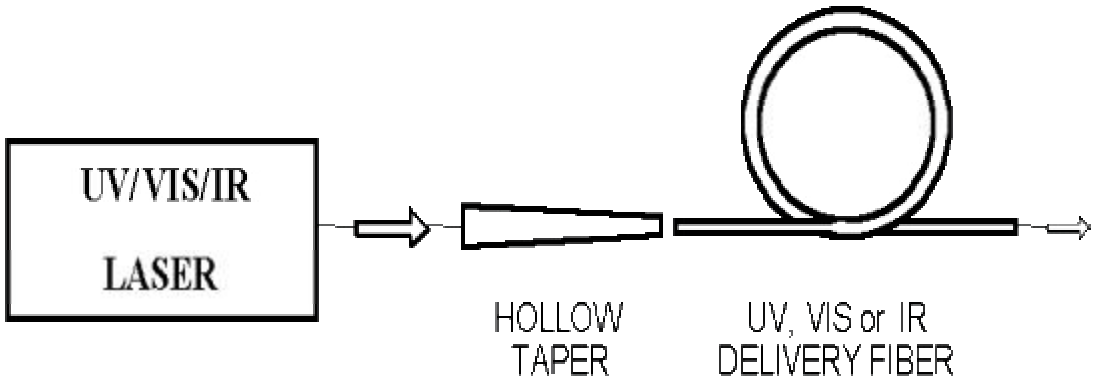


Figure 8. Hollow-taper based laser delivery bending for IR

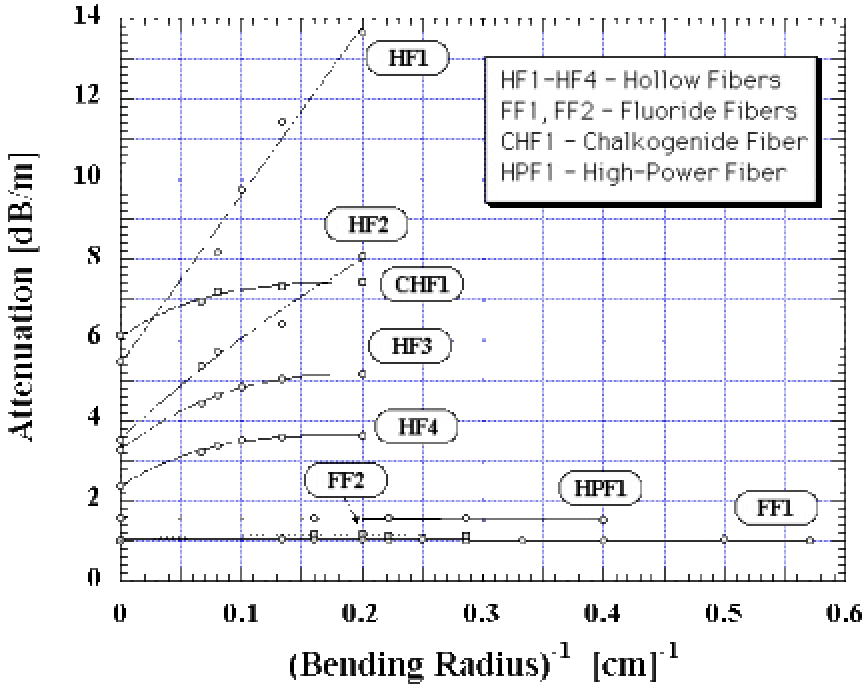


Figure 9. Graph of transmission vs. fibers and wavelengths

In another application, real-time measurements of biological parameters such as human blood serum, tissue, and other properties of organs can be facilitated with the use of carefully shaped and polished ends of optical fibers. Handheld, fiber-connected instruments capable of making direct and rapid optical measurements of tissues and fluids can be used for on-the-spot diagnosis. OST scientists have developed a series of optical sensors based on attenuated total reflection (ATR). Initially, a sapphire rod over-coated with paralyne (a widely used IR coating) was used. The distal ends were designed so that airborne radiation injected into the probe is reflected back toward the proximal fiber end. When touched to liquids or tissue, however, the radiation is coupled into the target tissue that the probe touches. Once energy is coupled into tissue, identification of the tissue can be made by analyzing the returned optical spectrum. These ATR devices are useful for liquid sensing, breath gas sensing, and for real-time monitoring of laser ablation processes.

Optical Phantoms in the Evaluation of Therapeutic Laser Medical Devices

Key words: phantoms, optical properties, laser ablation, performance

The Ho:YAG laser is used for a number of surgical procedures. For example, in urology, it is used for the lithotripsy of calculi and, in cardiology, it is used for transmyocardial revascularization (TMR) and percutaneous myocardial revascularization (PMR). In PMR, a catheter, housing a fiber optic system, is threaded through a small incision in the leg or groin, usually through the femoral artery, across the aortic valve, and into the left ventricle. The distal end of the fiber is placed directly against the ventricle's inside wall, and 8 to12 channels are ablated part way into the myocardium. Clinically, these channels have been shown to reduce a patient's angina and increase exercise tolerance. The actual biomedical mechanism for the success of TMR and PMR is still under investigation. Aside from damaging a valve and inducing arrhythmia, the main concern during PMR is completely perforating the myocardium instead of making partial channels.

In an effort to understand this ablation process, optical phantoms were developed in an attempt to match the optical properties and geometry of the targeted tissues. Since water is found in most soft tissue including myocardium, it is thought to be responsible for the absorption of the Ho:YAG laser radiation at 2.1 microns. Hence OST scientists developed an optical phantom of distilled water which was irradiated at varying path lengths to determine the amount of attenuation. The transmission of the laser radiation for these varying path lengths was measured. However, scattering, along with absorption, may also play a role in the tissue ablation process. After the water was exposed to the Ho:YAG laser radiation, quartz microspheres were added to the water and the process was repeated. The microspheres were added at a concentration that produced a scattering coefficient at the Ho:YAG wavelength that was similar to a value given in the literature. This was repeated at twice this concentration and again at three times this concentration.

The results indicated that the attenuation of the Ho:YAG laser radiation obeys Beers law, and with slope equal to the absorption coefficient. For the clear phantom, the slope was 2.638 mm^{-1}. A published value using a similar measurement scheme is 2.51 mm^{-1}. The slope for the water and scattering microspheres was 2.547 mm^{-1}.

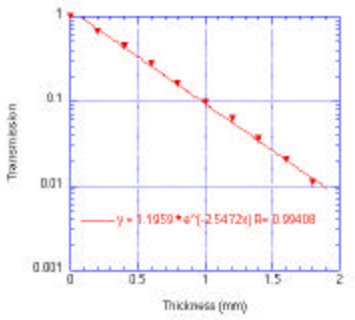


Figure 10. Ho:YAG transmission in distilled water and a 1% solution of silica microspheres (m_s=21.2 cm^{-1}) 22°C, 10 Hz, 550 micron diameter fiber

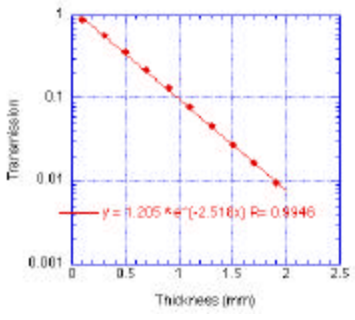


Figure 11. Ho:YAG transmission in distilled water and a 2% solution of silica microspheres (m_s=42.4 cm^{-1}) 22°C, 10 Hz, 550 micron diameter fiber

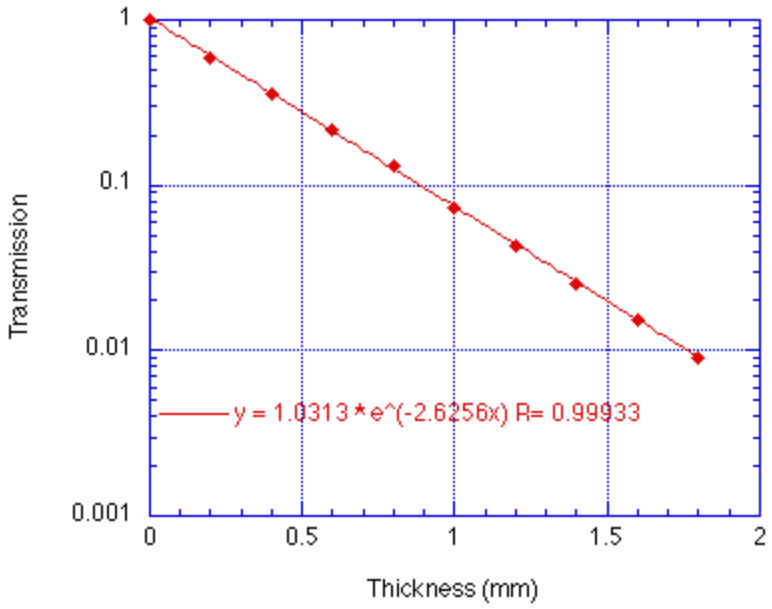


Figure 12. Ho:YAG transmissions in distilled water and a 3% solution of silica microspheres (m_s=63.6 cm^{-1}) 22°C, 10 HZ, 550 micron diameter fiber

While the slope for twice this scattering was 2.518 mm^{-1}, and the slope for three times this scattering was 2.626 mm^{-1}. These results indicate that scattering has little to no effect upon the attenuation of Ho:YAG laser radiation in water, and the absorption of water alone at the 2.1 micron wavelength can be used to determine the attenuation of the light intensity using Beers law.

OST scientists have also constructed ablation phantoms of agar (.5g/50ml of water). These phantoms have been formulated both with and without silica microspheres. They are being examined as a model for myocardial ablation. Researchers are measuring their ablation threshold and their ablation rates with the Ho:YAG laser. These rates will be compared to those of swine myocardial tissue. If acceptable, they will provide a reproducible ablative phantom for evaluating the performance of Ho:YAG lasers used in PMR.

MATERIAL DEGRADATION

Effects of Flex-Fatigue and Abrasion on Glove Barrier Integrity

Key words: gloves, accelerated aging, fatigue, abrasion

Natural rubber latex gloves that had been artificially aged in an oven at 70°C were subjected to biaxial flexing and viral challenge to assess barrier integrity. A unique fixed-displacement biaxial fatigue apparatus utilized an electrical signal to indicate a change in barrier properties, while permeability to virus was determined using a modified version of ASTM F1671-97a. The results indicated that unaged powdered and powder-free (nonchlorinated) gloves had significantly longer fatigue lives than unaged chlorinated gloves from the same manufacturer. Oven aging caused a significant increase in the fatigue life of the chlorinated gloves but only a marginal increase for powder-free gloves. When the electrical output during biaxial flexing did not indicate any change in barrier properties, no virus passage was found upon subsequent challenge with live virus. Conversely, when a change in the barrier properties was indicated by the electrical signal, virus passage was usually found. Viral permeability results for gloves that were not subjected to flexing indicated no degradation in barrier integrity due to oven-aging alone.

In recent years, there has been a tendency to seek alternative materials for medical gloves in order to preclude the occurrence of allergic reactions to the proteins found in natural rubber latex. This prompted the need to further study those alternative materials (neoprene, nitrile, tactylon™, and vinyl), so the biaxial flex fatigue apparatus was applied to test those materials as well. It was determined that the fatigue lifetimes for the alternative materials greatly exceeded those for natural rubber latex. It was also discovered that permanent deformation ("creep") was occurring with some of the material samples, namely vinyl and nitrile. Because of the fixed displacement nature of the biaxial flex fatigue apparatus, it was deemed that alternative testing methods needed to be pursued, i.e., abrasion, in order to gain benchtop performance data that correlated better with the rank-ordering of materials derived from clinical experiences.

OST scientists modified an in-house abrasion apparatus previously used to test polymeric cruciate-ligament replacements. Specifically, smooth-surfaced abrading bars and sample holders were fabricated out of stainless steel to allow for the testing of glove specimens of the same geometry as those used in the fatigue and viral permeability tests. Using a modified version of ASTM F1671-97a, aged and unaged samples (latex, neoprene, nitrile, tactylon™, and vinyl) are to be tested and their permeability to virus will be assessed again. Initial preliminary test results appear promising and will continue into FY 2000.

Pharmacokinetic Modeling of 4,4'-Methylenedianiline Released from Reused Polyurethane Dialyzer Potting Materials

Key words: modeling, hemodialysis

A hydrolysis degradation product, 4, 4'-Methylenedianiline (MDA), can be released from polyurethanes commonly used in medical device applications. MDA is mutagenic and carcinogenic in animals. In humans, it is hepatotoxic, a known contact and respiratory allergen and a suspected carcinogen. A physiologically based pharmacokinetic (PBPK) model was developed to estimate the absorption, distribution, metabolism, and excretion

of MDA in patients exposed to MDA leached from the potting materials of hemodialyzers. A worst-case reuse situation and a single-use case were investigated.

The PBPK model included five tissue compartments: liver, kidney, gastrointestinal tract, slowly perfused tissues and richly perfused tissues. Physiological and chemical parameters of a healthy individual used in the model were obtained from the literature. The model was calibrated using previously published kinetic studies of IV-administered doses of ^{14}C-MDA to rats. The model was validated using independent data published for MDA-exposed workers. The PBPK results indicated that dialysis patients who are exposed to MDA released from dialyzers (new or reused) could accumulate low levels of MDA and metabolites (total MDA) over time.

Validation of Proposed Revision to USP Physical Test 881 - Tensile Strength of Surgical Sutures

Key words: sutures, test method development

The test goals were to determine if the existing United States Pharmacopoeia (USP) suture strength tables were valid for the proposed revised test method, which allowed a variation in strain rate of about 30 % and to determine if the suture strength was a function of strain rate for the proposed range in strain rate. More than 20 different types of sutures encompassing the entire range of existing suture materials and sizes were tested. Tested sutures included three sizes of suture (6-0, 3-0, and 1) of the following types from three manufacturers, where possible: braided synthetic absorbable, monofilament synthetic absorbable, polypropylene, polyester, braided nylon, monofilament nylon, silk, gut, and stainless steel. Sutures were tested using three different sets of test parameters: new proposed USP specimen at high strain rate (16 min $^{-1}$), new proposed USP specimen at low strain rate (1 min^{-1}), and loop specimen at 20 mm/min., which corresponded to a strain rate at the low end of the range. All tested sutures met USP minimum strength requirements. Strength results for a number of suture types were statistically different for high and low strain rate tests. Loop results were generally the same or slightly less than the low strain rate results.

The results were presented to USP and the US Suture Industry Advisory Group (USSIAG). These data persuaded USP to amend the proposed revision to tighten the allowable variation in strain rate in the new test method. The new test method will be adopted July 1, 2000.

OPTICS

Intraocular Lenses

Key words: intraocular lenses, myopic implants, technical support

The intraocular lens (IOL) industry continues to develop new materials that are flexible enough to allow for folding. By folding the IOL, the lens can be inserted through a smaller incision, thus reducing the possibility of induced astigmatism. OST is assessing whether possible inclusions and bubbles in these new materials can produce unwanted optical effects. Such defects can cause the implanted lens to be the vision-limiting component of the visual system. OST performed laboratory tests on samples of soft IOLs made from these new materials. So far no defects have been found, and the optical quality of the lenses appears to be acceptable.

The null lens research project was brought to a close with the submission of a manuscript to a peer-reviewed scientific journal. This project evaluated the design of a null lens that would assist in the optical quality testing of a 20-diopter silicone IOL. When optical testing is performed in air, which is the industry standard, silicone IOLs pose special problems for the manufacturer. The index of refraction of silicone is lower than that of more commonly used acrylic. To produce the same refractive power in the eye, the silicone lens must have higher surface curvature. These higher curvatures result in significant spherical aberration when the lens is tested in isolation in air. Images formed in air with silicone lenses are not as clear as those formed with acrylic IOLs. Thus, silicone IOLs are commonly released with lower quality standards for resolving power in air. Unfortunately, the combination of spherical aberration and lower quality standards has the potential of allowing unwanted optical defects that may disturb vision after the IOL is placed in the eye. Results indicate that both the power tolerances and the optical resolution of the test silicone IOL are improved with the use of the null lens. Removing spherical aberration sharpens the focus, thus allowing optical power to be determined with greater precision and overall accuracy. Using a null lens to test the optical power of silicone lenses in air should result in more accurate vision quality for patients who receive these lenses.

Noninvasive Detection of Diabetes

Key words: diabetes, optical spectroscopy, noninvasive diagnosis

Approximately 16 million Americans have diabetes mellitus. One of the most threatening aspects of this disorder is the development of visual impairment due to cataract formation, diabetic retinopathy and glaucoma. Cataracts alone are 1.6 times more common in people with diabetes than in those without diabetes, and lens extraction is the only treatment. In many cases, diabetes-related ocular pathologies go undiagnosed until visual function is compromised. In order to develop techniques for early cataract detection, OST scientists are studying the progression of diabetes in a unique animal model and monitoring the changes in the lens using a safe, nondestructive dynamic light scattering technique. Dynamic light scattering (DLS) is commonly used by NASA in the characterization of macromolecular solutions in ground-based and microgravity protein crystal growth studies. This technique is proving to be a practical noninvasive diagnostic tool useful for the early detection of ocular pathologies. In the long term, it may be possible to predict diabetic status using DLS data obtained from the eye.

The animals used in the study are desert rodents, Psammomys obesus, commonly called sand rats. These animals are unique in that they develop diabetes is a manner similar to humans. DLS has been shown to discern subtle and diffusive changes in the lens of the diabetic sand rats during two months on a diabetogenic diet. The baseline data for the control and diabetic animals demonstrated two populations of particles, the majority of which were clustered in the 50-nm to 500-nm region. At of the end of the second month on diabetogenic diet, there was an overall shift in the distribution of the size and a change in intensity (quantity) of the particles in the lens. After two months on the diabetogenic diet, the majority of the particles were well above the 500-nm range.

Future studies using a larger sample size of both male and female sand rats will monitor the long-term effects of diabetes in conjunction with the blood glucose changes, glycosylated hemoglobin measures and insulin levels. Ocular and pancreatic histological changes over time will also be assessed. This combination of biochemical measurements, in vivo laser measurements and tissue microscopy will enable unprecedented documentation and correlation of the progression of the diabetic ocular pathologies.

Excimer Laser Ablation Studies

Key words: excimer laser, refractive surgery

OST scientists have been investigating the effects of low-fluence excimer laser irradiation on corneal tissue. This study was prompted by safety concerns of cumulative doses of low-fluence pulses potentially arising from poorly aligned or maintained refractive laser devices. The work was done in conjunction with personnel from CDRH's Office of Device Evaluation and colleagues at the Armed Forces Institute of Pathology (AFIP).

OST activities this year included the preparation of a manuscript based upon recent findings that bovine corneal stromal ablation occurs at a very low fluence of 10 mj/cm2. This fluence is below the published corneal ablation threshold for cow, rabbit, and human eyes, which ranges from 20 to 65 mJ/cm^2. The study demonstrated that 200 pulses at an energy level of 10 mJ/cm^2 ablated a thickness of 0.6 to 0.7 microns from the anterior randomly oriented layer of the cornea. These results demonstrate that excimer laser irradiation of the cornea at relatively low energy densities is not completely benign and that tissue removal and modification is occurring at these fluences. These findings add to the understanding of side effects of refractive laser surgery performed with devices that, due to misalignment or other opto-mechanical faults, deliver large numbers of low-fluence pulses to the eye.

Operation Microscopes, Endoilluminators, and Ophthalmic Instruments

Key words: operation microscopes, endoilluminators, ophthalmic instruments, cataract surgery, retinal injuries, standards

In past years, OST scientists have participated in studies on retinal photic injuries from operation microscopes and endoilluminators. While the number of patients exposed per

year to endoilluminators is substantially fewer than those exposed to operation microscopes, a more significant retinal injury may occur from endoilluminators than from operation microscopes. This is probably due more to the longer exposure times used during retinal surgery (where both an operating microscope and an endoilluminator are used) rather than in cataract surgery (where an operating microscope is used alone) and the larger spot size produced by the endoilluminator.

In prior years, OST conducted a laboratory evaluation of the risks of retinal photic injury from the optical radiation emissions from endoilluminators used during vitreo-retinal surgery. The results of this study were presented at an international symposium on the measurements of optical radiation hazards and also served as the basis for an agreement to develop a draft ISO optical radiation safety standard for endoilluminators. This study was concluded in FY 1999 with the evaluation of a newly developed endoilluminator that uses a uniquely filtered light source. A draft technical report was prepared and will be submitted for publication in a peer-reviewed scientific journal in FY 2000.

OST also initiated work to evaluate the use of short wavelength cut-off filters and an adjunct light source (in collaboration with ophthalmologists at National Naval Medical Center (NNMC)) for reducing the risks of retinal photic injury from operation microscopes. A number of different cut-off filters and fiber optic light sources were developed and evaluated using an operation microscope at NNMC. In this work, an ophthalmologist was asked to evaluate the quality of the light for both intensity and whether or not the color of the light was acceptable for a selected number of filter-light source combinations. A number of filter-light source combinations were rejected because the color of the light was not acceptable. In those filter-light source combinations, the light had an unacceptable yellow appearance. However, there were filter-light source combinations that were acceptable and that result is a significant reduction (at least 30 %) in the risks of retinal photic injury during cataract surgery.

This project was conducted in collaboration with ophthalmologists at the NNMC. The data obtained will be used in the ANSI and ISO standards development process for ophthalmic instruments. It is expected that the use of these standards will result in a reduction of the risks of retinal injuries from these devices and assist in the review of premarket applications.

Pulsed Xenon Lamps

Key words: optical radiation, optical standards

In 1998, OST initiated work, in collaboration with the US Army Center for Health Promotion and Preventive Medicine (USACHPPM) at Edgewood Arsenal to measure and evaluate the optical radiation emissions from products that use pulsed xenon lamps. Initially, a laboratory-based spectroradiometer was developed to measure the integrated spectral radiance of pulsed light sources. This spectroradiometer was used to evaluate several pulsed Xenon lamps having the potential to expose the public to hazardous levels of optical radiation. Due to difficulties in transporting some of these sources to the laboratory, it became necessary to develop a spectroradiometer that was portable and

could be transported to measure products in the field. Two additional pulsed xenon lamps were tested using the field instrumentation. Preliminary evaluation of the data indicate that the optical radiation emissions from two of the lamps exceed safety guidelines by a factor of about two in the normal mode of operation. However, while the optical radiation emissions exceed the safety guidelines, they do not necessarily present an imminent public health hazard because of the safety factor of about 10 built into the guidelines.

RISK ASSESSMENT

Microbial Risk Assessment

Key words: infection, microbial risk assessment, dose-response models, Sterility Assurance Levels

Mathematical dose-response models are required to estimate the incidence of infection following exposure to low doses of infectious microorganism on a piece of suture material. Initially, the ß-Poisson and single-hit models were used for this purpose. In 1999, OST scientists collaborated with scientists at NCTR to employ a suite of models to conduct high-to-low dose extrapolation for microbial effects. This more robust assessment reduces uncertainties in assessing the risk posed by patient exposure to low numbers of microorganisms on suture material.

Development and Evaluation of a Swine Model to Assess the Preclinical Safety of Mechanical Heart Valves

Key words: mitral valve replacement, mechanical hearts, swine model

This study was conducted in collaboration with the Department of Surgery (Experimental Surgical Services), School of Medicine, University of Minnesota to assess the utility of a swine model for the evaluation of the thrombotic potential of mechanical prosthetic heart valves. Twenty-two swine underwent mitral valve replacement using three different bileaflet mechanical valve designs. Each animal was placed in one of three anticoagulation protocols (Group I- International Normalized Ratio, INR, of 3.0-3.5; Group II- INR of 2.0-2.5; and Group III- no anticoagulation). Out of the 22, 21 animals survived the immediate postoperative period. Of 13 animals receiving anticoagulation, 10 died from hemorrhagic complications (hemopericardium) within the first 30 days of the study. Eight of nine animals not receiving anticoagulation survived for long-term evaluation. All valves from the long-term survivors exhibited marked fibrous sheathing. Perivalvular defects and organized thrombi were also observed in valves explanted from the long-term survivors. Difficulty in maintaining safe levels of anticoagulation (resulting in a high incidence of hemorrhagic complications), marked fibrous sheathing and associated thrombosis, and a high incidence of perivalvular defects were significant factors limiting the utility of this model.

Risk Assessment of Dioxin in Tampons

Key words: risk assessment, dioxin, tampons

OST scientists have developed a risk assessment that examines the potential for harmful effects to occur following exposure to dioxin released from tampons. Concerns began to be raised in the press and Congress because most tampons contain rayon made from cellulose fibers that might contain dioxin due to the manufacturing process of the rayon. Chemical analysis of tampons previously published indicated that little or no dioxin was present; however, there were small amounts of structurally related compounds present. OST scientists evaluated the reports of the chemical analysis, usage patterns and exposures, and calculated the risks from tampon use--both in a "most likely" exposure scenario and in a "worst case" exposure scenario. In neither case was the amount of exposure from tampons significant.

Average Annual Solar UV Dose of Continental US Citizens

Key words: ultraviolet, UV-emitting, cancer, solar dose

The average annual solar UV dose of continental United States citizens is not known but is required for relative risk assessments of skin cancer from UV-emitting devices. OST calculated this dose using a novel approach. The EPA's "National Human Activity Pattern Survey" recorded the daily outdoor-activity profiles over the course of 2 years for about 10,000 continental US citizens to assess exposure to environmental pollutants, one of which is UV radiation. From that survey, OST extracted only the daylight-hour data of the northern and southern indoor workers, subdividing by seasons, sex, and age (0-21, 22-59, and 60+) to find the average time Americans spend outdoors in each group. Using the ambient percentage for indoor workers found by the Dutch (2.5%; H. Slaper thesis, 1987) to standardize the northeastern data, OST scientists found their actual UV-exposure time was about one-third their total daylight-time outdoors. Of the total available solar UV, the average US citizen's ambient percentages are as follows: northern females 2.67% and males 3.54%, southern females 2.56% and males 3.79%. OST then calculated the subjects' average annual solar UV dose, excluding vacation, using seasonal averages from measurements made over a 2-year period by spectrophotometers located in four quadrants of the US: Atlanta, Georgia, Boston, Massachusetts, Bozeman, Montana, and Riverside, California. Including a conservative 3-week vacation in the continental US, i.e., 30% country, 30% beach, 30% sight-seeing and 10% home, the estimated average annual solar UV doses are as follows: northern females 28,361 J/m2 and males 32,479 J/m2, southern females 33,215 J/m2 and males 39,834 J/m2. The average annual solar UV dose for the continental US citizen is 25,169 + vacation (9,178), or 34,347 J/m2 (343 SED or 137 MED, MED=250 J/m2). Thus, scientists can now assess the relative increased risk of skin cancer from UV-emitting devices for the continental US citizen.

STANDARDS DEVELOPMENT

The participation by CDRH in the development of consensus test methods and performance standards for medical devices and radiological products encourages participation by other sectors of the medical community and enables the Center to impact the final outcomes, insuring that Agency needs are met by these documents. This activity is focused in the Office of Science and Technology. Our standards program includes: managing the program for the Center; serving as liaison to the committees of the several Standards Development Organizations that are relevant to this sector; laboratory development of information in support of test method development; and, partnering with the industry and academia in the execution of interlaboratory studies of test methods to establish their precision and bias. The Standards Program Coordination Staff, OST (SPCS), accredits the Center's liaison members of standards committees. SPCS coordinates the activities of the Center's Specialty Task Groups (STGs) and manages the development of the Center's consensus position of individual documents balloted by the various Standards Development Organizations (SDOs). **Table 12** illustrates the level of effort dedicated to the standards program in 1999 in comparison with previous years. In addition, OST staff contributes directly to the development of standards by volunteering to develop the first draft of many standards considered by the Office and Center. **Table 13** is an illustrative list of these documents developed this year. **Table 14** is a listing of the Interlaboratory Studies in which OST participated, and **Table 15** shows the new test methods developed. Finally, OST staff is actively engaged in the overall management of the standards program of the various SDO committees that are important in the development of medical device standards. **Table 16** shows the contribution of OST in committee management in 1999.

Table 12 – Consensus Standards – Level of Effort Comparison

	1996	1997	1998	1999
Liaison Reps – CDRH	224	225	230	240
- OST	60	59	63	68
Standards efforts – CDRH	487	492	509	498
- OST			214	152
Standards trips – CDRH	98	115	109	163
- OST (US)	29	37	51	54
- OST (int'l)	25	21	10	20
- OST (people)	30	29	34	35

Table 13 - Consensus Standards - Significant Contribution as an Author of New or Revised Guidance

Sunlamps – IEC
Risk Management – ISO/IEC
Fundus Camera – ISO
Operating Microscope – ISO
Ophthalmic Instruments – ISO
Aneurysm Clips – ISO
Ethylene Oxide Residuals – AAMI
Sterility Assurance Level – AAMI
Endotoxin Levels (LAL) on Medical Devices - AAMI
MR Compatibility of Implant Materials and Devices – ASTM
Selecting Generic Biological Test Methods for Materials and Devices - ASTM F 748
Assessment of Hemolytic Properties of Materials – ASTM F756
Short-term Screening of Implant Materials - ASTM F 763
Assessment of Compatibility of Biomaterials for Surgical Implants with Respect to Effect of Materials on Muscle and Bone - ASTM F 981
Pulse Oximeter – ASTM F1415, ISO 9919
Particle Characterization - ASTM F 1877
Testing for Biological Response to Particles In-Vitro - ASTM F 1903
Testing for Biological Response to Particles In-Vivo - ASTM F 1904
Resorbables - ASTM F 1983
Complement Activation - ASTM F 1984
Characterization of Alginate for use in Tissue Engineered Medical Devices – ASTM
MR artifact size for implants – ASTM
Extraction of Latex Proteins Using the Lowry Method - ASTM
Extraction of Latex Proteins Using the ELISA Method – ASTM
Suture Tensile Strength – USP
People Scanners – ANSI
Action Spectrum for Photocarcinogenesis – CIE
Testing Protocols for Photocarcinogenesis – CIE
Guidance on the Selection of Reference Materials – ISO 10993-8
Sample Preparation and Reference Materials – ISO 10993-12
Bone Screws - ASTM F 543
Medical Device Software Engineering - AAMI

Table 14 - Consensus Standards - Interlaboratory Studies for Determination of Precision and Bias

Evaluation of Hemolytic Properties of Materials – ASTM F756
Ethylene Oxide Residuals - AAMI
Glove Powder – ASTM
Chemical Accelerator Residual on Gloves – ASTM
Latex Soluble Proteins – ASTM
Latex Condom Thickness – ASTM
Extraction of Latex Proteins Using the ELISA Method - ASTM

Table 15 - Consensus Standards - New Test Method Development

Glove Powder – ASTM
Chemical Accelerator Residual on Gloves – ASTM
Test Methods for In-Vitro Blood Glucose Monitoring Systems

Table 16 - Consensus Standards - Committee/Subcommittee/Working Group Leadership Positions

AAMI
- Standards Board – Jim McCue
- International Standards Committee – Don Marlowe
- Awards Committee – Don Marlowe
- Apnea Monitoring Committee – Jeff Silberberg
- ECG Electrodes – Dave Daly
- Software – John Murray
- Sterilization Standards – Vicki Hitchins
- Electromagnetic Compatibility (EMC) Committee – Jeff Silberberg

AIUM
- Technical Standards Committee – Hector Lopez
- Digital Measurement Subcommittee – Hector Lopez

AIUM/NEMA
- Joint Output Standards Subcommittee – Gerald Harris

ANSI
- Government Members Council – Mel Altman
- Executive Standards Council Audit Subcommittee – Mel Altman
- Medical Device Standards Board – Jim McCue
- EMC – Patient Connected Devices WG – Howard Bassen
- N43.17 – Radiation Safety for X-ray Security Scanners – Frank Cerra

ASTM
- Board of Directors – Don Marlowe
- Committee on Technical Committee Operations – Dan Chwirut
- E48 – Biotechnology
  - E48.02 – Characterization and Identification of Biological Systems – Larry Bockstahler
- F04 – Medical and Surgical Devices and Materials
  - General Interest Vice Chairman – Dan Chwirut
  - F04.12 – Metallic materials
    - F04.12.05 – Nitinol – Dan Chwirut
  - F04.13 – Ceramic Materials – Gary Fischman
    - F04.13.04 – Polycrystalline Alumina – Gary Fischman
    - F04.13.71 – Magnesia Stabilized Zirconia – Gary Fischman
    - F04.13.18 – Beta TCP – Gary Fischman
  - F04.15 Subcommittee on Test Methods – Dan Chwirut
    - F04.15.08 – Coating Abrasion – Gary Fischman
    - F04.15.11 – MRI Compatibility – Terry Woods, chair Marlene Skopec, secretary
  - F04.16 Biocompatability Testing – Kathy Merritt

F04.16.01 – Response to Particles – Kathy Merritt
F04.16.06 – Response to Polymers –Kathy Merritt
F04.16.08 – Immune Response: Complement – John Langone
F04.16.09 – Characterization of particles – Stan Brown
F04.18 – Device Retrieval & Analysis – Stan Brown
F04.19 – Corrosion – Stan Brown
F04.19.01 – Corrosion Fatigue Testing – Stan Brown
F04.19.02 – Corrosion of Modular Interfaces – Stan Brown
F04.19.03 – Method for conducting Cyclic Polarization Potentio-dynamic Polarization Measurements for Corrosion Susceptibility – Stan Brown
F04.21 – Osteosynthesis – Don Marlowe
F04.21.01 – Bone Screw Performance Standard – Don Marlowe
F04.30 – Cardiovascular Devices
F04.30.05 – Interventional Devices – Dan Chwirut
F04.33 – Surgical Instruments
F04.33.01 – Puncture Resistance of Sharps Containers – Pat Dubill
F04.40 – Tissue Engineered Medical Products – Grace Picciolo
F04.93 – Orthotics and Prosthetics – Don Marlowe
F12.60 – Security Systems and Equipment – Don Witters & Jon Casamento

IEEE

SCC28 –SC1 – Radiofrequency Radiation Hazards, Measurement & Computations techniques – Howard Bassen
SSC34 – Certification of Radiofrequency Safety – Wireless handsets Howard Bassen
C63 SC8 – Medical Device EMC (patient connected WG) – Howard Bassen

IEC

TC56 - Dependability
TC62C – High Energy Equipment & Nuclear Medicine Equipment – Tom Heaton
TC87 WG 9 – Ultrasound Performance Measurements – Hector Lopez

ISO/IEC

Joint Working Group on Risk Management – Harvey Rudolph

ISO TC 168 – Orthotics and Prosthetics – Leader, US Delegation, Don Marlowe
ISO TC 172 SC 7 WG 6 – Ophthalmic Instruments – Bob Landry
ISO TC 194 - Biological Evaluation of Medical Devices – Leader, US Delegation – Don Marlowe
WG 2 – Degradation - Ed Mueller
TG – Biodegradation of Ceramics – Gary Fishman
WG 12 – Sample Preparation and Reference Materials – Don Marlowe
WG 14 – Material Characterization – Joseph Hutter
WG 15 – Chemical Based Toxicology Assessment – Mel Stratmeyer

NCCLS

Delegate – Jim McCue
Nominating Committee – Jim McCue
Area Committee on Automation – Chares Furfine
Area Committee on Immunology and Ligand Assay
Subcommittee on Digoxin – Maralyn Lightfoote
Area Committee on Molecular Methods – L. Bockstahler, Kiki Hellman

WHO International EMF Project International Advisory Committee – Russell Owen
International Commission on Non-ionizing Radiation Protection, SC 2 – Biology and Medicine – Russ Owen

Apnea Monitor Physiologic Waveform Test Method Development

Key words: apnea, physiologic waveforms, standards, test methods

The Apnea Monitor Physiologic Waveform Test Method Development project is intended to provide CDRH and the medical device community with a standard bench test method for determining the ability of an apnea monitor to detect apnea (the cessation of breathing) and its pathophysiological consequences. In this effort, OST engineers are working with clinicians and manufacturers through a committee of the Association for the Advancement of Medical Instrumentation (AAMI), the Apnea Monitoring Committee, which is co-chaired by the CDRH representative. This multi-year development project consists of the following steps:

- Design, development, and construction of a real-time signal and data acquisition system for recording and displaying high-fidelity physiologic waveforms (signals) from infants in sleep labs.

- Collection (recording) of a comprehensive set of physiologic waveforms (signals) from infants in clinical sleep labs.

- Annotation of the collected waveforms by a panel of experts.

- Assembly of the annotated waveforms into a database.

- Design, development, and construction of physiologic parameter simulators to play back the recorded physiologic waveform database to the sensors of the apnea monitor under test. The recorded waveforms will be used to control electrical and mechanical simulators of the physiologic parameters. These simulators will be connected to the apnea monitor under test in place of the patient.

In FY 1999 prototype signal acquisition software and hardware (see **figure 13**) were completed and tested for the following ten channels:

Signals to be used for testing monitors:
- transthoracic impedance
- ECG
- end-tidal CO_2
- expired/inspired air temperature
- two channels of inductance plethysmography (rib and abdomen)

Signals to be used for annotation:
- two channels of pulse oximetry signals (SaO_2 and pulse wave)
- two channels of “calibrated” inductance plethysmography (rib and abdomen)

Signals from all 10 sensors were acquired simultaneously from an adult volunteer, and the data were transferred successfully from the UNIX-based acquisition computer to a laboratory PC.

Figure 13. Real-time signal and data acquisition system for recording and displaying high-fidelity physiologic waveforms (signals) from infants in sleep labs

Completion of acquisition hardware included fabrication and testing of analog-to-digital converter (ADC) subsystems, including signal conditioning and serial data transmission, for six of the channels: impedance, ECG, end-tidal CO_2, expired/inspired air temperature, and two channels of pulse oximetry signals (SaO_2 and pulse wave). Hardware for the four-inductance plethysmography channels was completed and tested in FY 1998.

Investigational Review Board approval for pilot clinical signal acquisition was renewed at the Pediatric Sleep Disorders Center (PSDC, formerly SIDS Institute), University of Maryland Medical Center (UMMC), Baltimore, Maryland.

The acquisition system was transported to the UMMC and demonstrated to PSDC personnel. Modifications necessary to provide required signals to PSDC equipment were determined and started.

ASTM MR Safety and Compatibility Test Methods Development

Key words: MR compatibility, test method development

OST scientists continued to work on developing standard test methods for determining the safety and compatibility of implants and medical devices in the magnetic resonance (MR) environment. A standard test method for determining magnetically induced displacement force on implants passed ASTM subcommittee ballot and will be issued for main committee ballot in 2000. Two other standard test methods for determining image artifact and **rf** heating of implants will be released for ASTM subcommittee ballot in 2000.

ASTM Committee F-04 Tissue Engineered Medical Products (TEMPS)

Key words: tissue engineering, standards

Over the past 2 years, approximately 40 task groups have started to develop standards for medical products containing cells, biomaterials or biomolecules to repair or replace human tissue. This process has occurred within the official standards organization, the ASTM in Committee F-04 Medical and Surgical Implants and Materials in Division IV Tissue Engineered Medical Products.

This group of approximately 130 scientific, regulatory, and industrial persons has established an effective communication system, with several web sites, organizational structure, and standards processing mechanisms for achieving consensus. FDA reviewers participate in this process to facilitate future recognition of the standards for regulatory use. A CDRH staff briefing highlighted the development of a general classification draft for TEMPS, a TEMPS' substrate guide, terminology drafts, and an alginate characterization draft. OST staff participated in the organization of the two biannual ASTM TEMPS meetings and a series of satellite meetings at the Gordon Research Conference, Holderness, Massachusetts.

Endovascular Stent Standards Development

Key words: stents, test method development, standards

OST laboratory personnel, in collaboration with ODE and industry and under the auspices of ASTM, are developing detailed test procedures for clinically relevant engineering attributes of endovascular stents. Test methods for recoil, radial force, crush, securement, corrosion, and trackability are being validated on six different stent designs.
This laboratory effort supports a larger collaborative activity with the Health Industry

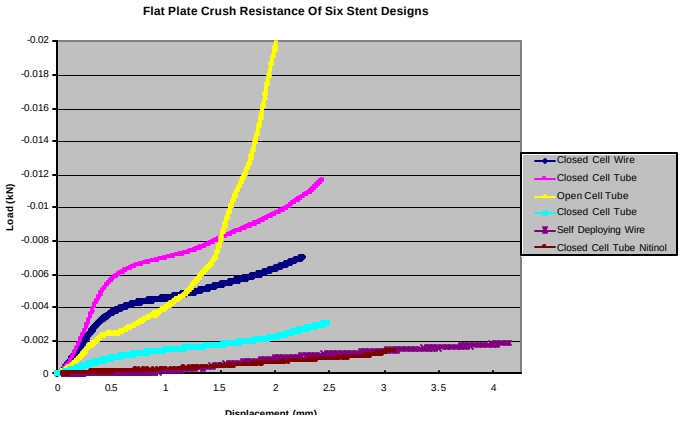


Figure 14

Manufacturers Association (HIMA) and ASTM that could result in expedited clinical trials for endovascular stents. HIMA is collating a database of clinical outcomes from all stent clinical trials and developing the appropriate clinical endpoints for stent designs with certain engineering characteristics. The ASTM Interventional Cardiology Task Group, co-chaired by OST and with the data generated by the OST laboratory effort, is developing standardized test methods for the engineering characteristics that differ among stent designs. Differences in engineering characteristics, measured by uniform procedures, may help explain the differences in clinical outcomes.

Modification of ASTM Standard Test Method F1671 for Detection of Small Tear Latex

Key words: latex tears/holes, ASTM test method modification

A modification to ASTM Test Method F1671-97b, Test Method for Resistance of Materials Used in Protective Clothing to Penetration by Blood-Borne Pathogens Using Phi-X174 Bacteriophage Penetration as a Test System, was developed to allow detection of small tears in elastic materials. The original method provides for a flat, open-mesh restrainer to prevent expansion of elastic material. While latex test specimens with open, laser-drilled holes ($\geq$ 1 micron) fail this test by allowing virus penetration, specimens with small tears (30-90 microns) pass. A restrainer of molded stainless steel screen with a hemispherical portion provided controlled expansion and allowed detection of the defective specimens with small tears.

Development of a Standard Practice for Testing for Alternative Pathway Complement Activation in Serum by Solid Materials

Key words: alternative pathway, complement activation, standards

Complement is a series of serum proteins involved in mediating immune reactions. Complement activation is a tightly regulated process, which, in addition to direct cell cytolysis, can have profound affects on the immune, vascular, and coagulation systems. Though complement activation is an important defense mechanism of the host, particularly against microbial infections, inappropriate activation (such as by implanted or external medical devices which encounter human blood) may result in serious acute or chronic reactions.

Complement activation can occur by two main pathways: the “classical” pathway and the “alternative” pathway. The classical pathway is triggered by antibodies bound to a cell surface. The alternative pathway is triggered by free hydroxyl or amino groups, such as those present on microbial organisms. If medical device materials activate complement, it will most likely be by the alternative pathway. Confirmation that complement activation by a candidate material is via the alternative pathway adds further weight to the material’s potential to trigger inappropriate complement activation when implanted in a patient or placed in contact with the patient’s blood outside the body.

OST scientists are developing a Standard Practice that screens specifically for alternative pathway complement activation by solid materials used in the manufacture of medical devices. This supplements ASTM Standard Practice F1984-99, also developed by OST scientists, which screens for complement activation but does not specify which pathway caused the activation.

Examples of devices whose materials might activate complement by the alternative pathway include perfusion devices (such as dialysis membranes, cardiopulmonary-assist systems, biosensor membranes, liver-assist perfusion devices, and columns for removing antibodies and other factors from patient blood), indwelling artificial vascular grafts, encapsulated drugs or cells, and vascular shunts/stents/catheters. OST scientists are conducting research to acquire baseline information related to assessing risk from inappropriate complement activation, particularly via the alternative pathway, by these devices.

A microassay was developed for assaying the ability of human serum to lyse target rabbit red blood cells (RBCs) via the alternative complement pathway. Optimized conditions included cell and serum concentrations, calcium and magnesium concentrations, and physical exposure parameters. Confirmation of alternative pathway activation was obtained by immunoassay for the complement split products C4d and Bb. C4d is unique to the classical pathway while Bb is unique to the alternative pathway. Control reagents were zymosan (a yeast cell wall component) and HAGG (human aggregated gamma-globulin.) Zymosan is a specific activator of the alternative pathway while HAGG activates the classical pathway. Nonspecific lysis was determined using sensitized rabbit RBCs, heat-inactivated complement, and complement depletion using zymosan. Control responses were compared to the representative device material Sepharose. Sepharose is a matrix material in antibody-absorbing columns used to treat patient blood.

Next, a variety of methods were explored for rapid screening of alternative pathway depletion by solid materials. The optimum method involved exposing device materials to genetically deficient serum for a critical component of the classical pathway. The method involves exposing C4-deficient guinea pig serum to a solid material, removing the material, and then assaying the exposed serum with the rabbit RBC alternative pathway assay for remaining complement activity. Only materials that activate complement by the alternative pathway will deplete complement function from the C4-deficient serum.

Presently, the screening method is being validated by testing a variety of representative device materials and control substances for complement depletion. Following validation, this method will be submitted as a draft Standard Practice to the ASTM Committee F-4 on Medical and Surgical Materials and Devices via Subcommittee F04.16 on Biocompatibility.

Radiation Safety Standard for Personnel Security Screening Systems

Key words: security screening, x-ray.

OST provides a representative to the American National Standards Institute's Accredited Committee N43 on Equipment for Non-Medical Radiation Applications. In 1999 OST proposed and obtained approval for a new N43 standard dealing with the use of x-rays for non-medical screening of people. The standard is intended for systems used to detect contraband and weapons carried by individuals. These systems are made possible by new technology that uses a small fraction of the radiation dose common in medical diagnostic radiology. There is a potential for exposing large human populations to ionizing radiation from this new source. CDRH staff convened a task group to start work on a standard that will set limits on the dose delivered. OST provides the chairperson for this task group, which held its first meeting in November 1999. OST is currently working on a measurement protocol to be incorporated into the standard.

Sterilization, Reuse, and Package Integrity

Key words: sterilization, reuse, package integrity

OST scientists have participated in various AAMI working groups on such sterilization issues as chemical sterilants, steam sterilization, microbiological methods, packaging, ethylene oxide sterilizers, ethylene oxide sterilization residues, sterility assurance levels, and bacterial endotoxin test methodologies. AAMI has held several conferences and has working groups on the issue of reusing single-use and reusable medical devices. OST scientists have participated in these conferences, having contributed posters, given talks, and chaired sessions.

AAMI has a working group that is involved in writing standards on packaging for sterile medical devices. OST scientists are participating in the working group involved in rewriting the standard and have contributed to evaluating methods that may be suitable for examining seal integrity and possible leaks through packaging materials.

Standard Methods for Evaluating the Blood Damage Potential of Materials Used in Medical Devices

Key words: hemolysis testing, blood damage, cardiovascular medical devices, and standards

The materials used in blood-contacting medical devices (e.g., oxygenators, tubing, catheters, and artificial hearts) are evaluated for biocompatibility using a battery of cell-response tests. These tests include an in vitro assay developed over 25 years ago to determine the material's chemical potential in destroying red blood cells (hemolysis). Researchers are reviewing the usefulness of the current hemolysis standards as part of the CDRH effort to recognize usable testing standards for manufacturers that demonstrate safe and effective performance of their materials and devices.

In FY 1999, OST worked with nine industry laboratories on Phase II of a project to revise and validate the most widely used standard for hemolysis testing (ASTM F756 - "Standard practice for assessment of hemolytic properties of materials"). This document is the basis for the international standard on hemolysis testing of medical devices (ISO

10993-4: Part 4, Annex D) and is also referenced by pharmacopoeias for toxicity testing of pharmaceutical plastic containers. The goal of this project is to create a revised standard test that is easy to perform, appropriate for all materials, sensitive, reproducible, and indicative of a patient's response to the material.

The basic hemolysis assay consists of placing a test sample of material taken from the finished, sterilized device into a test tube containing buffered, isotonic saline and diluted rabbit blood. The tube is incubated at 37 ° C for up to 3 hours, at which time the material is removed and the saline is obtained by centrifugation. The percentage of hemoglobin that has been liberated into the saline from damaged red blood cells is quantified using a spectrophotometer.

The OST team performed experiments to identify important test parameters that could affect the results of the assay. Interestingly, it was found that increasing the blood concentration in the tubes did not necessarily increase the percentage that becomes damaged by hemolysis. This may be due to the necessity of having the red blood cells near to the surface of the material where chemical leachables can affect them. Microscopic studies of red blood cells exposed to hemolytic material particles demonstrate that damaged cells can release hemoglobin but remain intact by resealing their membranes. These hemoglobin-deficient cells, known as "ghost cells," surround the particles and act as a physical barrier that prevents viable cells from getting close to the material. The importance of allowing the red blood cells access to the surface was also demonstrated in an experiment where a test material was enveloped by blood clots. These prevented red blood cells from getting close to the surface and again depressed the hemolysis caused by that material. One method currently being investigated to avoid these spatial exclusion problems is the preparation of chemical extracts from the test materials. The extracts are obtained by heating the materials while they are being bathed in saline or cell serum. Then, only the extract is introduced to the red blood cells.

In 2000, OST will participate in the planning and testing of the Phase III interlaboratory study to further explore the critical parameters which need to be controlled to make a useful standard. This includes evaluating the following: different blood anticoagulants, media solutions, blood concentrations, material surface areas, time course of damage, positive control materials, use of extracts from materials, reproducibility of the test within and between laboratories, chemical factors which can alter red blood cell membranes or can interfere with the measurement of hemoglobin, biologic variability of blood from different animals, and the interpretation of hemolysis test results. Along with other concurrent OST projects, the results of this study will help to better define the in vitro test limits for evaluating chemically and mechanically induced hemolysis by devices and to determine their safe use in patients.

Evaluation of the Standard Tests for Neurological Shunts

Key words: neurological shunts, CSF shunts, hydrocephalus, in vitro performance testing

A Systematic Technology Assessment of Medical Products (STAMP) committee was formed to address problems associated with neurological shunts used to treat

hydrocephalus. This committee was managed by CDRH's Office of Surveillance and Biometrics with staffing from various Offices, including OST. The problems addressed include infection, mechanical shunt failure, obstruction, over- and under-drainage, migration, and user error. On January 8, 1999, CDRH sponsored a one-day conference entitled, "Cerebrospinal Shunt Technology: Challenges and Emerging Directions" at the National Naval Medical Center in Bethesda, MD. Over 140 attendees from medical, patient, industrial, and government groups were present to consider the main focus of the conference. A summary of the conference can be found at www.fda.gov/cdrh/stamp/shuntconf.pdf

The conference demonstrated that there is a fundamental lack of information on the underlying physiology and function of cerebrospinal fluid (CSF). CSF shunts used to treat hydrocephalus may not address the underlying disease process but may merely help alleviate the symptoms of increased cranial pressure and enlarged cerebral ventricles. In addition, neurochemical factors within the CSF may inadvertently be destabilized by the diversion of excess fluid from the brain and central nervous system.

Regarding the performance of CSF shunts, a wide range of testing has been carried out and reported by several groups. These groups, particularly those in Germany and the United Kingdom, have evaluated shunts under various conditions: steady and unsteady (pulsatile) flows, high and low pressures, with and without gravitational effects, in the presence or absence of proteins, and with and without siphoning. All of these tests show inconsistencies in the performance of CSF shunts for their labeled application and that CSF shunts routinely fail to meet specifications. Unfortunately, these in vitro test results do not appear to be predictive of clinical performance. Therefore, the specification of proper selection and specification of engineering tests remain an issue.

Currently, there exists ASTM standard F647-94: Standard Practice for Evaluating and Specifying Implantable Shunt Assemblies for Neurosurgical Applications. This standard is not universally applied to test the performance of CSF shunts because of its limitation to steady-flow conditions. Additionally, manufacturers are not willing to subject their devices to a standard that may not sufficiently evaluate the presumed advantages incorporated in their designs. OST is attempting to clarify the physiological test parameters needed for an appropriate performance evaluation of CSF shunts in order to develop a more suitable in vitro test methodology and, thus, a better standard.

Examination of Mechanical Prosthetic Heart Valve for an Acoustic Signature of Cavitation

Key words: prosthetic heart valves, cavitation, acoustic energy

Transient cavitation has been observed near operating mechanical heart valves. This cavitation, the formation and very rapid collapse of tiny bubbles, can cause valve damage and induce hemolysis. Thus, CDRH's Draft Replacement Heart Valve Guidance Document asks for in vitro testing to evaluate a valve's potential for producing cavitation. This usually involves using high-speed photography or video imaging to examine the

valve immediately after closing, and to look for tiny bubbles near the valve as a function of the force with which the valve closes. However, since the collapse of these bubbles can produce broad-spectrum acoustic energy, it might be possible to detect cavitation by 'listening' to the noise produced by valve closing.

Previous studies in OST have indeed shown that high-frequency sound, into the 100's of kilohertz, is produced when cavitation is present. These same studies also indicated, however, that cavitation could not be deduced simply from the presence of this energy, since the closing of the valve, even in the absence of cavitation, also produced energy extending into this region. The more force with which the valve closes, the more energy is shifted into higher frequency ranges and, also, the more likely it is that cavitation will be present.

A new study, examining the acoustic output spectra of several different valves under a broad range of closing conditions (with and without cavitation present) is currently underway. This study utilizes an oscillating fluid piston-driven system to open and close the valve. The cycle rate and pressure forcing the valve shut is variable. A hydrophone is used to detect the acoustic energy produced, and a high-speed video system is used to independently check for cavitation. The purpose of this current study is twofold. First, it is to examine the spectra of several different valves under conditions producing no cavitation in order to determine conclusively whether high-frequency energy is present. This is important because, in spite of FDA's earlier study, researchers and industry are utilizing the mere presence of high frequency noise as proof of cavitation being present. The second reason is to use the data collected under non-cavitating conditions, together with extensive data taken under valve-closing conditions causing cavitation, to develop criteria to determine the presence of cavitation by acoustic emission alone.

To date, the acoustic emissions of six mechanical valves (two each of three different designs) have been examined under varying non-cavitating conditions. High-frequency acoustic energy has been found present up to 350 kHz, the exact spectrum of which varies from valve to valve and with different closing conditions.

Sterility Assurance Levels

Key words: infection, sutures, SAL, standards

OST scientists have completed a project to determine the adequacy of sterility assurance levels (SAL). This work has now been published in the *Journal of Biomedical Materials Research* 44: 261-265, 1999. The risk of infection was approximately 6% when only a few (<10) organisms were on the device at implantation using a mouse model. An AAMI standard for SALs, needed for materials that undergo degradation with the more extensive sterilization procedures usually required for medical devices, is being developed using the data from this study as a major consideration. This standard is in the ballot stage. OST scientists are contributing to the writing of the draft standard, which will also cover manufacturing operation validation and routine monitoring.

International Standards Development

Key words: ethylene oxide, international standard, guidance

Additional guidance for the use of an international standard on residues of ethylene oxide (AAMI/ANSI/ISO 10993-7) was submitted for publication in the February issue of Medical Devices and Diagnostic Industry (MDDI). This publication should help industry and government reviewers better determine the appropriate levels of residues for ethylene oxide and ethylene chlorhydrin on sterilized medical devices. The publication also compares the residue levels, as determined by this international standard, to the levels that have commonly been used for almost two decades, as determined by the 1978 FDA Proposed Rule.

Tissue Engineering

Key words: program development, standards/guidance, technology monitoring, education/training

Biotechnology advances account for the expanding development of new medical products such as engineered tissues and biohybrid devices, diagnostics for genetic and other disorders, and drug and vaccine delivery systems. CDRH's biotechnology coordination program and the FDA InterCenter Tissue Engineering Working Group (TEWG) develop programs and regulatory approaches to ensure appropriate assessment and oversight of biotechnology products.

The Center Coordinator for Biotechnology and Chair of the TEWG has provided leadership in establishing programs to provide guidance and planning options to the Center and Agency which encompass 1) technology monitoring and assessment, 2) evaluating applications in medical products, 3) standards for tissue-engineered medical products, 4) education/training for Agency review/research staff and the scientific community at large, and 5) science and regulatory policy recommendations. Several products continue to provide a strong knowledge base for CDRH/FDA and to facilitate scientific and regulatory assessment of new biotechnology-derived and tissue-engineered medical products (TEMPs). These products include the following:

- the Spring 1999 and Winter 1999 Tissue Engineering Course, the fourth in the FDA Staff Colleges Course Series on Tissue Engineering;
- draft standards for TEMPs through ASTM Division IV: TEMPs of Committee F04 (Chair of TEWG serves as Division Secretary and primary FDA liaison for Division IV) - 10 active subcommittees have been established with a total of 40 different task groups, each developing at least one draft standard;
- maintenance of the FDA InterCenter Biomaterials Compendium, a database inventory of TEMPs;
- organization and participation in several national and international biotechnology and tissue engineering forums such as the ASTM biannual meetings and Rice Institute Tissue Engineering Course; and

- publications on tissue engineering science and regulatory issues, such as book chapters in Principles of Tissue Engineering, Second Edition and Toxicity Assessment Alternatives.

To facilitate communication and enhance cooperation across Federal agencies in tissue engineering science, the Center Coordinator for Biotechnology initiated the establishment of the Multi Agency Tissue Engineering Science (MATES) Working Group, with members from NSF, DOD, DOE, and NASA. The goals of the working group are to

- facilitate communication across departments/agencies and the tissue engineering research and development (R&D) community by regular information exchanges/meetings and a common web site;
- enhance cooperation through co-sponsorship of scientific meetings/workshops and participation in standards development; and
- monitor technology by undertaking cooperative projects and studies, such as a study on the global assessment of tissue engineering R&D.

Ophthalmic Standards Support

Key words: ophthalmic instruments, standards, medical devices

OST continued to actively participate in developing ANSI and ISO performance standards for the quality of the optical radiation emissions from ophthalmic diagnostic instruments, operation microscopes, and endoilluminators. In 1997, ISO adopted a quasi-horizontal standard for ophthalmic instruments (ISO 15004). In 1998, a number of product specific standards for ophthalmic instruments were adopted. They include standards for Chart Projectors (ISO 10938), Slit Lamps (ISO 10939), Fundus Cameras (ISO 10940), Direct Ophthalmoscopes (ISO 10942), Indirect Ophthalmoscopes (ISO 10943), and Synoptophores (ISO 10944).

Proposals for New Work Items to prepare separate draft ISO standards for the light hazards and mechanical/optical performance for operation microscopes (Draft Standard for Optical Radiation Safety -ISO/DIS 10936-1 & 2) were submitted to national committees for approval in 1998. In 1999, ISO/DIS 10936-2 was resubmitted for a second Draft International Standard DIS vote because of the many comments received on the first DIS vote.

The draft standard for Endoilluminators - Draft Standard for Optical Radiation Safety – was submitted to ISO for circulation as a Committee Draft (CD) to national committees for approval. This standard was approved as a CD, and was submitted for a vote as a DIS. OST performed standards conformance assessments of the ISO ophthalmic instrument standards for use in the new CDRH 510(k) paradigm. Parts of these standards were deemed appropriate for use in 510(k) clearances for all diagnostic ophthalmic instruments.

A proposal for a New Work Item to prepare amendments to ISO15004 - Ophthalmic Instruments for a separate draft ISO standard for the light hazards from ophthalmic instruments was submitted to national committees for approval in 1998. There was an

affirmative vote. One purpose of the amendments is to develop ultraviolet and infrared radiation limits based on fundamental biological data in concert with the International Conference on Non Ionizing Radiation Protection (ICNIRP) to accommodate ophthalmic instruments using new light sources with higher effective color temperatures. A second purpose is to develop amendments to distinguish clearly nonhazardous ophthalmic instruments (such as the tear scope) from the potentially hazardous instruments (such as slit lamps). The proposed schemes for accomplishing these goals were presented at the annual ISO TC172 meeting in Europe by OST Scientists. An amended draft standard will be circulated for a vote as a Committee Draft in 2000. OST scientists assumed a leadership role in developing the proposed amendments to these standards.

Guideline for the Detection of *Mycobacterium Tuberculosis* and other Pathogenic Mycobacteria by the Polymerase Chain Reaction Procedure

Key words: guideline, standard, Mycobacterium tuberculosis, polymerase chain reaction, PCR

An OST molecular biologist led the development of an ASTM guideline for the detection of *Mycobacterium tuberculosis* (MTB) and several other pathogenic mycobacteria by the polymerase chain reaction (PCR) procedure. This guideline (E 2048 “Standard Guide for Detection of Nucleic Acids of the Mycobacterium Tuberculosis Complex and Other Pathogenic Mycobacteria by the Polymerase Chain Reaction Technique”) was developed by ASTM Committee E-48 on Biotechnology in collaboration with DIN (Deutsches Institut fuer Normung = German Institute for Standardization) Committee E3/E9 on Molecular Biological Detection of Mycobacteria.

PCR is a tool used in molecular biology and biotechnology laboratories for the rapid and sensitive detection sequences of DNA and RNA. The guideline can be used for the detection of mycobacteria in any molecular biology or biotechnology laboratory, and it has information useful for both beginners and those experienced in performing PCR. The guideline should also be useful to aid in the detection of mycobacteria in clinical, diagnostic laboratories. It is recommended that this “microorganism-specific” PCR guideline be used in conjunction with ASTM’s “general” PCR guideline (E 1873, published in 1997). The combination of the two guidelines provides recommendations, basic considerations, criteria, and principles that should be helpful when developing, utilizing or assessing PCR procedures and specific protocols for the detection of the DNA or RNA of specific mycobacteria. The mycobacteria-PCR guideline was recently approved by ASTM and will be published early in 2000.

Alginate in Tissue-Engineered Medical Products

Key words: Tissue Engineered Medical Products (TEMPS), alginate, ASTM, standard test methods, standards

Alginates are used in many applications, including encapsulating islets of Langerhans for treatment of Type I diabetes, biodegradable urethral stents, and sustained drug release systems. However, impure alginate can be fibrotic to cells. The Mannuronic form of the

alginate is suspect as the causative agent of the fibrotic response. Most of the alginate is not fully characterized as to the endotoxin levels, impurities, the M/G ratio, the source or the viscosity. The source of the fibrotic reaction in well characterized alginates and whether human monocytes/macrophages produce a fibrotic response to alginates is under investigation. Literature searches are being performed to determine if suitable standard test methods are available which can be used to characterize alginates.

Chemiluminescence and cell biological assay techniques, which can serve as standard test methods in cases where such methods are not available, are being developed in OST/DMMS. The Alginate ASTM Task Group (F04.43.04) is developing ASTM standards for the characterization of alginates used in Tissue Engineered Medical Products. Extensive work at the November 1999 ASTM meeting in Kansas City, Missouri, and a satellite Alginate Task Group ASTM meeting March 2000 in Rockville, Maryland, has led to the development of a draft standard, submitted for balloting at the May 2000 ASTM meeting in Toronto, Canada. The draft is entitled, “Standard Guide for the Characterization and Testing of Alginate for Use in Biomedical and Tissue Engineered Medical Product Applications”.

TECHNICAL SUPPORT

Book of Hazards

Key words: device hazards, risk management

The Book of Hazards is an Intranet tool designed to collect and improve utilization of CDRH's institutional knowledge of medical device hazards.

Medical device safety issues require consideration of a host of factors involving hazard identification, risk estimation, and mitigation techniques. Over time, individual CDRH reviewers and analysts have gathered a great deal of valuable information regarding medical device hazards associated with the devices in their area of specialization. Other reviewers may not be aware that this information exists, may not understand its importance or applicability to other cases, or may not know where in the Center to find the information in a timely fashion. Some interchange does occur via informal networking, seminars, meetings, and even happenstance; but there is currently no established formal mechanism for documenting and sharing such information, leading to inefficiency and inconsistency in the quality of reviews.

This project is intended to develop a shared database application, residing on the CDRH Intranet, to collect and make the following information available:

- patient and/or user exposure to the salient hazards of a device;
- consequences resulting from those hazards;
- risks associated with the hazards;

- techniques used by manufacturers to mitigate hazards; and
- any residual risks.

The information is organized and cross-referenced by device type, technology (e.g., embedded software, pneumatics, and patient-contacted electrodes), clinical specialty, general hazard, or other desired field. The intent is that each time a device is analyzed, the reviewer/analyst may draw upon the Center's knowledge base by querying the system for hazards that have been identified in the past. The reviewer can then concentrate on determining the risks associated with the identified hazards in each particular case and on identifying new hazards that were not previously recognized. These new hazards would be submitted to the system, thereby improving the completeness and applicability of the knowledge base. As a quality assurance measure, an appropriate technical committee would review new hazard information for accuracy and completeness before it is entered into the Intranet database.

A prototype model for the Book of Hazards has been procured under contract. This web-based application is designed to walk a user through the process of entering data into the Book of Hazards and retrieving it. The prototype is a research tool designed to explore what parameters are essential to capture, how the information should be organized to allow for efficient capturing, how it should be organized for retrieval, and how reviewers and analysts identify salient information related to hazards in their daily routine. Three groups of reviewers/analysts have been enlisted to "test drive" the prototype. Experience to date shows that while these target groups find the Book of Hazards to be a useful tool, OST facilitation is still necessary for accurate data entry. To date, there is still insufficient data within the Book of Hazards to serve as a stand-alone tool. Current efforts focus on improving the organization of hazard information, updating the hierarchy of hazards to reflect the latest standards (IEC 14971), and developing new concepts for future prototypes, such as using local, next level, and end effects to describe consequences. OST is working with industry and academic experts to examine each field and determine what is useful information and how it should be captured, organized, and displayed.

One finding of this research so far is that many people support the concept of a Book of Hazards but few find the time to enter hazard information as a routine matter. It is clear that the Book of Hazards cannot achieve its full potential unless the collection of important information is made to be part of a reviewer's routine tasks. In an agency such as FDA – whose main product is decision-making – the raw material most essential to make decisions is information. It is the effective use of information that is at issue here. Pulling together databases into a consolidated architecture is a very, very difficult process. To some extent, this is being done with administrative processes such as timekeeping, leave tracking, etc through the EASE project. In the not-too-distant future, CDRH will have to develop an equivalent integrated application suite for managing regulatory activities. This suite will allow data generated by one functional unit to be shared and used by another. For example, data from a PMA relating to safety (that is, the hazards) will be captured and communicated to the group responsible for surveillance, as a starting point. This information may also be of use in investigating the root cause of failures that result in

a recall. An enterprise-wide information architecture will describe who uses what data and for what purpose.

A global view of how information flows from one process to another, and within each process, is needed as a framework for the Book of Hazards tool. This vision of an information architecture is necessary for this tool to meet expectations since it is, in essence, a cross-linking of existing information stores from a database of unique device identifiers and through identification of device hazards, causes, and consequences. An information systems architecture description is even now more important with the pressure of international harmonization.

Proposed New Wireless Medical Telemetry System to Minimize Risks from Electromagnetic Interference (EMI)

Key words: electromagnetic, interference, telemetry, physiological, monitor, radio, spectrum

OST engineers continued to address the issue of interference of wireless medical telemetry systems (WMTS) by various signals within the same radio frequency band. This electromagnetic interference (EMI) can disrupt the monitoring of vital patient physiological information. Wireless medical telemetry systems communicate vital patient information via radio transmissions between a patient-worn physiological monitor and a remote central monitoring station. The WTMS allows the patient to be ambulatory without being encumbered by direct-wire connections to the monitoring devices. Under the present Federal Communications Commission (FCC) rules for use of the radio spectrum by WTMS, these medical signals must accept interference but not cause it to the primary FCC-licensed spectrum users (e.g., radio, TV broadcasters).

OST engineers helped formulate a proposal submitted by the American Hospital Association (AHA) to the FCC to create separate radio frequency spectrum bands for use by wireless medical telemetry. In July 1999 the FCC formally voted to create the Wireless Medical Telemetry Service and published a Notice for Proposed Rulemaking with draft rules for its use. This proposed rule marks the first time in the United States that wireless medical telemetry signals will be afforded protections from interference on par with the primary licensed spectrum users. The new frequencies for telemetry systems, with appropriate coordination among users, will drastically reduce the potential for EMI to these vital medical systems from intentional transmitters such as television stations.

Development of an In Vitro p53 Gene Mutation Assay for Cancer Risk Studies

Key words: mutation, p53 gene, tumor

There is a great need for more relevant tests for safety evaluation of medical device materials and radiation-emitting devices, such as cellular phones, in relation to human cancer risk. Recent findings in cancer research have shown that substantial proportions of human tumors have mutations in the p53 tumor suppressor gene, 50% on average, but varying by tumor type. These mutations cause loss of genome integrity and cellular

growth control, and are causally related to cancer development. Evidence indicates that the mutations found in human tumors can arise from environmental exposures.

In assessing cancer risk, therefore, one important question is whether a biomaterial, breakdown product, impurity or other relevant substance or device has the capability of causing mutations in critical regions of the p53 gene. Currently available studies for pre-clinical safety evaluation cannot determine this. An OST scientist is adapting a new technique for assessing p53 mutations in a plasmid vector harbored in yeast. The special yeast strain, constructed at MIT, is engineered to respond to the mutant phenotype with a color change. In an FDA lab, conditions are being worked out that enhance the practicality of the assay for routine screening purposes. Another goal is to determine to what extent the assay detects the mutations seen in human tumors and at what doses of standard carcinogenic substances. The results will also be compared with the p53 transgenic animal assay. An assessment can then be made of the potential for the assay to replace existing assays or provide new information, such as a quantitative assessment of likely effects in humans at the doses to which they would be exposed. Collaborators on this project include scientists at the WHO's International Agency for Research on Cancer (IARC), which maintains the world-wide human tumor p53 gene data base.

FDA-Wide Genetox Network

Key words: genetic toxicologist

An OST scientist has spearheaded the organization of genetic toxicologists from all of the centers. The Genetox Network meets monthly, addressing standards issues and specific questions from reviewers related to product assessment. In a little more than 6 months, the group has addressed a number of FDA and international standards for preclinical genetic toxicology assessment: ISO revision at CDRH, the draft VICH standard at CVM, ICH maintenance issues at CDER, and the revision of CFSAN's Redbook. The group has also been involved in training reviewers through course lectures in several Centers' staff colleges and through a check-sheet for CFSAN reviewers implementing the new regulations for food contact substances. The group is addressing a current controversy in genetic toxicology: the requirement for testing at toxic doses of the test article. What levels of toxicity are desirable, and are there levels that cause false positive results? How can potential "threshold doses" be determined? Members of the group participate in and sometimes lead scientific societies in the area of toxicology or genetic toxicology. These activities involve integration of new scientific results, revision of testing protocols and other standards, development and adoption of new technologies, and interaction with the regulated industry.

Noncoherent Optical Radiation Program

Key words: UV radiation, calibrations, technical support

During 1999, OST continued to provide support to the optical radiation compliance program through consultations on optical radiation measurements. The OST laboratory maintains equipment for conducting high precision optical radiation measurements.

Laboratory measurement instrumentation is calibrated using a standard of spectral irradiance, which has been calibrated by NIST. To assure the validity of measurements made by OST, periodic intercomparisons are also conducted with NIST, and in-house quality assurance procedures are followed.

FDA's Winchester Engineering and Analytical Center (WEAC) assists the Center in performing measurements of light sources collected from manufacturers and other field locations. In 1999, CDRH/OST completed an intercomparison with WEAC. Measurements on identical sources at the two laboratories were found to be within acceptable parameters.

Laser Field Compliance Program

Key words: lasers, calibrations, product testing, technical support

During FY 1999, OST continued to provide support to the laser field compliance program through consultations on optical radiation measurements. The activities of OST's laser calibration laboratory provide validity to the measurements of compliance testing programs nationwide. The OST Laser Calibration Laboratory maintains equipment for conducting high precision optical measurements. The laboratory measurement standard is a C-series calorimeter built by NIST. To assure the validity of measurements made by OST, periodic intercomparisons are conducted with NIST, and in-house quality assurance procedures are followed. In 1999, a formal laser measurements intercomparison with NIST was begun at the helium neon laser wavelength (632.8 nm). Work on the intercomparison at other laser wavelengths will continue into FY 2000.

Laser Product Evaluations

Key words: lasers, product testing, technical support

OST continued to provide support to CDRH's Office of Compliance through the laboratory evaluation of laser products. The testing is normally performed in order to confirm the manufacturer's classification of a specific product. During FY 1999, OST evaluated 11 laser pointers that had been obtained either from the manufacturer or from samples of products being detained at the port of entry. Eight products were continuous wave red laser pointers, and the other three products were pulsed, operating in the green wavelength range. All of the pointers tested were confirmed to meet the Class IIIA limit of the laser product performance standard. OST has also evaluated eight continuous wave red laser pointers to compare the results of measurements performed at CDRH with those performed at the Winchester Engineering and Analytical Center (WEAC). The results are comparable within the estimated uncertainties. Three infrared laser rangefinders were also evaluated in the OST laboratory. These products were found to meet the Class I limit of the laser product performance standard, as required.

Laser Standards Support

Key words: lasers, tracheal tubes, medical devices, patient protective covers, standards

OST continues to provide support to voluntary standards activities through participation on the ANSI Z136.4 and ISO TC172/SC9 committees. In ANSI Z136.4, a draft measurement standard has been submitted to the ANSI executive committee for comment. In general, the document was favorably received. There were some additional comments that will soon be addressed. The document provides guidance for measurement procedures used in evaluating the hazards associated with lasers and optically-radiating diodes and is intended for use when the hazard classification of the product is either unknown or when it has been changed due to product alteration.

In ISO TC172/SC9, work continues on standards for determining the laser resistance of the shafts of tracheal tubes. A standard was published in 1999. It was agreed within TC172/SC9 that upon publication of the standard, a New Work Item would be initiated to address comments received when the document was circulated as a Draft International Standard [DIS]. This has been done, and the 1999 ISO standard is now being modified. The document is now at the stage of a Committee Draft. The work on a standard for surgical drapes and patient protective covers suitable for use in laser surgery is also progressing. Significant feedback was received on the draft document, and these comments are now being addressed.

Sunlamps: FDA Publishes an Advanced Notice of Proposed Rulemaking (ANPRM)

Key words: sunlamps, risk assessment, melanoma, amendments to performance standard

FDA announced its intent to propose amendments to the performance standard for sunlamp products on February 9, 1999. The agency took this action to address the following concerns: the adequacy of the warnings on sunlamp products, the current recommended exposure schedule to minimize risk to customers who choose to produce and maintain a tan, current labeling for replacement lamps, and current health warnings that do not reflect advances in photobiological research. FDA solicited comments and information from interested persons concerning the subject matter of the proposed amendments.

Twenty-seven submissions were received in response to the Advanced Notice of Proposed Rulemaking (ANPRM). They came from the indoor tanning industry, lamp manufacturers, dermatology societies, academia, salon owners, state and county governments, and one insurance company. No new data on a possible melanoma-sunlamp connection was received. New data on the safety of the current FDA-recommended exposure schedule was obtained which showed that no injury resulted from this schedule; but tans did not appear in some subjects until after 6-8 sessions. The industry thought that this was a problem, in that customers are paying for a tan and not getting one until several sessions had passed. There was general agreement that sunburns are hazardous, but there was considerable controversy over whether a tan was harmful or helpful in that it protected against sunburns and melanoma development. There were major disagreements over the "benefits" of UV exposures. OST's suggestions of possible changes for replacement lamps, warning statements in catalogs, specification sheets and brochures, informed consent statements, and increased educational efforts won widespread support.

CDRH briefed the Technical Electronic Product Radiation Safety Standard Committee (TEPRSSC) on September 15, 1999, the indoor tanning industry on November 4 and 5, 1999, and the Federal Council on Skin Cancer Prevention on December 8, 1999. CDRH informed these groups that several conclusions had been reached, including:

It is premature to conduct a risk assessment of possible malignant melanoma from sunlamp exposures because of inadequate dose response data, insufficient human data, and poor action spectra for melanoma development. The only good risk assessment for humans is for increased squamous cell carcinoma.

FDA has decided that there is no immediate crisis with regards to possible melanoma development from sunlamp use and, therefore, has decided to delay publishing amendments to the performance standard to allow the Agency time to evaluate the effectiveness of two important ongoing actions:

The indoor tanning industry has initiated new steps in enforcing existing regulations and recommendations on sunlamps, including education on recommended exposure scheduling, advice on replacing spent lamps, educating salon operators, use of consumer consent forms, and establishing working relationships with national and international standards organizations.

Several international standards organization, such as the International Electro-technical Committee (IEC), are developing recommended consensus standards for sunlamps which will address most of the concerns expressed in the Agency ANPRM. These international standards should be available in the near future for the Agency's evaluation.

The CDRH Working Group on Sunlamp Amendments proposes that the Center wait for at least a year in order to work with the indoor tanning industry and the international standards organization. After that time period, FDA will evaluate the effectiveness of the above two efforts and then decide on a future strategy for drafting a Proposed Rule.

Surgeon and Patient Examination Gloves

Key words: surgical gloves, latex allergens, protein levels

Experimental and clinical studies demonstrate that cornstarch on surgical gloves can enhance foreign body reactions, increase infections, and act as a carrier of natural latex allergens. OST has provided leadership in defining the issues and developing a proposed rule to address these adverse health effects. The proposed rule, published in the 7/30/99 FR, would

1) reclassify surgeon's and patient examination gloves from medical device class I to class II;

2) reclassify gloves into four categories (powdered and powder-free surgeon's gloves; powdered and powder-free patient examination gloves); and

3) introduce special controls, including

   a) -new label caution statements that include recommended maximum limits for protein (1,200 micrograms), glove powder (120 mg), and powder-free residue (2 mg)
   b) labeling of protein levels on NRL gloves

   c) labeling of powder levels on powdered NRL and synthetic gloves

   d) expiration date labeling supported by stability studies

The public comment period closed on January 28, 2000. OST will continue to provide the leadership to respond to the comments and finalize the rule.

Guidance on the Implementation of the Biomaterials Access Assurance Act of 1998

Key words: Biomaterials Access Assurance Act, guidance document

During 1999, a committee chaired by OST drafted a proposed guidance document on the implementation of the Biomaterials Access Assurance Act of 1998 (BAA98). Included with the document was a draft of a proposed Federal Register notice for the guidance, including the proposed paperwork requirements of this guidance. The final package was vetted among the Center Offices for review before submission to the Federal Register by the Good Guidance Practices (GGP) liaison within the Office of Compliance. As the Office of Compliance would most feel the impact of BAA98, it was decided that they should be the office following GGP procedures when finalizing the submission of the guidance.

X-ray Calibration Laboratory

Key words: calibration, x-ray measurement, laboratory accreditation.

OST is responsible for the traceability to National Standards of ionizing radiation measurements made by FDA or used in FDA compliance programs. This mission is fulfilled by the operation of a secondary standard laboratory accredited by the National Voluntary Laboratory Accreditation Program (NVLAP). In fiscal year 99 a total of 1551 accredited calibrations of radiation measuring instruments were performed by irradiation in known x-ray fields. In addition, 741 electrical pre-calibration of instruments, 125 calibrations of non-invasive kVp meters and 105 calibrations in special radiation beams were performed. Since many state agencies perform FDA inspections and sometimes use their own equipment, states rely heavily on this CDRH calibration service. In FY 99 66% of the calibrations were for instruments owned by FDA, 30% for instruments owned by state agencies, and 4% for instruments owned by other federal agencies. 62% of the instruments calibrated were designated for testing compliance with the Radiation Control for Health and Safety Act of 1968. 38% of the instruments were designated for testing compliance with the Mammography Quality Standards Reauthorization Act of 1998. OST

keeps track of approximately 2800 pieces of equipment at over 500 inspector stations throughout the country and U.S. territories, instrument usage and calibration data. As required by NVLAP, the laboratory this year has participated in a Proficiency Test administered by the National Institute of Standards and Technology (NIST), has undergone an internal audit of operating procedures, and conducted a comprehensive review of the Quality System. A major revision of the quality manuals was undertaken in FY 99, resulting in the computerization of the manuals. These documents are now available on the CDRH Intranet as well as on CD-ROM. The laboratory complies with NIST Special Publication 812: *Criteria for the Operation of Federally Owned Secondary Calibration Laboratories (Ionizing Radiation);* NIST Handbook 150: *NVLAP Procedures and General Requirements;* and ISO Guide 25: *General Requirements for the Competence of Calibration and Testing Laboratories.*

X-ray Calibration Laboratory Computer System

Key words: calibration, Linux, NT, GESPAC, OS9, mammography, metrology, NT server

The CDRH X-ray Calibration Laboratory applies computer technology in all aspects of the calibration process. During the past year, OST has continued its efforts to apply additional computer automation by (1) upgrading computer systems and application software, (2) developing new databases and procedures for inventory control, and (3) implementing a local area network to transfer data between the various OST computers within the Radiation Metrology Branch (RMB).

Some of the implementation plans were interrupted while the computer equipment was updated to ensure Y2K compatibility and to provide consistency with FDA initiatives, assuring proper functioning of computers in 2000. This effort included

- installing an upgraded network (twisted pair);
- converting all RMB users to upgraded computer systems running under the NT operating system;
- installing upgraded NT servers (450Mhz) for improved performance;
- installing appropriate service patches for software to ensure proper performance in the year 2000; and
- installing the latest version of software on the GESPAC systems, the systems used for controlling the facilities used in the calibration of radiographic instruments.

In some instances, the Y2K-related activities led to changes in the original plans to automate the control of the calibration facilities:

- The RMB server functions were changed to improve overall performance in obtaining, using, and archiving data. One server, the Data Server, is now the repository of all data obtained from measurements at each calibration facility **(figure 15)** as well as data used for shipping, reports, and other RMB functions.
- A second server, the Application Server, is where the RMB website, http://rmb.cdrh.fda.gov, is maintained. This server, in a separate building from the

Application Server, holds backup data from files that reside on the Application server.

- A third server, a Linux Server, is now used for several computer services that run more efficiently on this system instead of the GESPAC systems. Two examples are the print functions and the barometric pressure measurement functions.
- Special software is required on NT servers before data can be transferred from the GESPAC systems that use a unique "real-time" capable operating system (OS9). The vendor of that software no longer supports the functions RMB requires; but the Linux operating system software does, and OST testing showed that the Linux Server provides for more accurate and rapid transfer of data from the GESPAC system. Although the Linux operating system is a completely different platform, it appears to computer systems using the Microsoft NT operating system as another "NT" system. Therefore, OST data archiving procedures could be simplified and did not have to be platform-dependent.
- Finally, additional printers were purchased to replace older ones that do not have the capabilities necessary for use with the new GESPAC systems, workstations, and servers that were added as part of the Y2K-related upgrades.

In FY 1999, RMB began publishing operation manuals to the Center's Intranet (http://rmb.cdrh.fda.gov). Additionally, all the Quality Manuals are available at that site, which is part of the activities necessary for NVLAP mammography accreditation.

New laboratory-specific systems were installed and checked for Y2K compatibility. These systems enable OST/RMB to perform ancillary activities such as making CD-ROM copies of data and reports, scanning images of documents unavailable in electronic form, testing and developing new computer programs and hardware, and performing data analyses necessary for research programs in progress.

OST began beta testing on the various subsystems of the complete automation system, with finishing this testing by the second quarter of FY 2000 as the goal. Beta testing included

- backup and restoration procedures for all data. (copies of archive data will be stored off-site;
- all computerized procedures necessary for maintaining the inventory of calibrated instruments for the Federal, state, and local government, including reports;
- quality control data procedures; and
- programs and procedures relegated to the laboratory-specific systems.

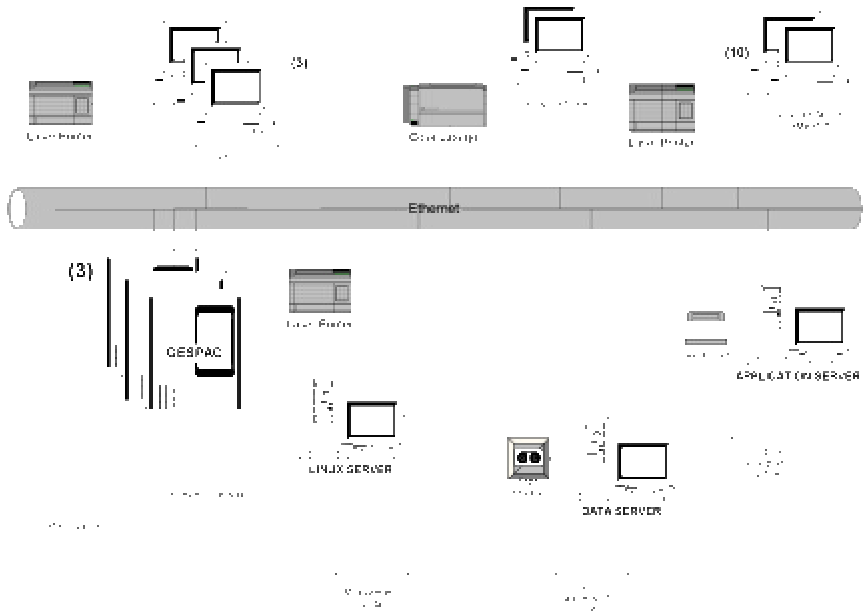


Figure 15. Local Area Network

Microwave Oven Instrument Calibrations

Key words: Microwave Oven Performance Standard

During FY 1999 OST calibrated a total of 68 microwave survey instruments in conjunction with enforcing the FDA Microwave Oven Performance Standard. The bulk of these instruments were calibrated for the FDA field offices (29 units) and the state and local health agencies (18 units) that work closely with the field offices. The remaining instruments were calibrated in the precision anechoic chamber and used to calibrate OST's Electrophyiscs Branch mass calibration facility.

In addition to the calibrations, OST designed and purchased a new computer control system for the mass calibration. The fall 1999 calibrations were performed using the new system, but development will not be fully complete until 2000.

ULTRASOUND

Improved Ultrasound Contrast-Detail Phantom

Key words: diagnostic ultrasound, image quality, contrast-detail, phantom

The Contrast-Detail ultrasound phantom, developed by OST staff, has been included as part of a draft international standard for evaluating ultrasound imaging systems and has been sold worldwide for many years. One of the drawbacks of the original phantom, however, was the lack of sufficient image sampling for each contrast level and target diameter. To solve this problem, an improved version of the Contrast-Detail phantom has been designed and constructed.

The new phantom was designed in OST and is specifically intended for use with the computational observer, a computer-based image evaluation method also developed in OST. The new phantom allows for improved statistics and better error analysis in computing the signal-to-noise ratio for each target size and contrast. The completed prototype was built for OST by a commercial laboratory and was delivered late in 1999. Testing of the prototype phantom for compliance with specifications is scheduled during fiscal year 2000. If testing demonstrates a successful design, this phantom will be submitted to both national and international standards organizations as a tool for evaluating ultrasound image quality.

Medical-Use Hydrophone Calibration Via Time-Delay Spectrometry

Key words: ultrasound, exposimetry, hydrophone

Miniature ultrasonic hydrophones are the primary measurement devices used to characterize the acoustic pressure fields produced by medical diagnostic ultrasound transducers. Because of the broadband nature of the pressure pulses, particularly when distorted by commonly observed nonlinear propagation effects in water, the hydrophone's response should be known over a wide range of frequencies extending down to approximately 100 kHz. Otherwise, significant errors could occur in measuring the peak rarefactional pressure, an important quantity for assessing the likelihood of cavitation onset, and the Mechanical Index, a related quantity displayed on diagnostic ultrasound equipment that gives an indication of the potential for mechanical damage to exposed tissues. However, at present, hydrophone sensitivities below 1 MHz are rarely reported because of the lack of suitable calibration techniques. Three-transducer reciprocity and laser interferometry have been used in this frequency range, but these are time-consuming single-frequency techniques. A more efficient method developed by OST engineers that employs broadband, plane-wave pulses of known spectral content has been used successfully; however, the sensitivity of this method is low because of the unfocused, nonresonant operation of the source transducer.

A calibration procedure that overcomes both of these deficiencies involves the swept-frequency technique known as time-delay spectrometry or TDS. However, in the past,

TDS has been used for hydrophone calibrations only at frequencies above 1-2 MHz. Therefore, a calibration system based on TDS, but designed to operate at frequencies from approximately 100 kHz to 2 MHz, was successfully developed and tested. In this approach, the digitized TDS response of a 'reference' hydrophone, i.e., one having a known frequency response, was subtracted from the response of a 'test' hydrophone to be calibrated. This procedure results in an efficient method of producing sensitivity plots over the entire frequency range. To utilize the ability of TDS to furnish a calibration over a wide frequency range in one measurement for each source-receiver combination, it is desirable to have a broadband source transducer. A variable thickness (plano-concave) transducer design was demonstrated to be a useful source, because its response does not have the minimum at twice the fundamental frequency that is characteristic of a constant-thickness transducer. The results of this study have been published in both print and Web-based versions of a peer-reviewed scientific journal, and they are influencing both Center 510(k) guidance and international ultrasound measurement standards.

Ultrasound Bone Densitometry

Key words: ultrasound, bone density, osteoporosis

In the last two years, FDA/CDRH has approved the first three PMA's for ultrasound bone densitometers. Several other submissions are currently under review. This is a new technology, which is likely to undergo much technological evolution and regulatory activity in the near future. Currently there is a considerable lack of standardization among devices.

Approval for a clinical project entitled “Development and Validation of Ultrasonic Backscatter Measurement for Bone Density Assessment” (funded by the FDA Office of Women’s Health) was obtained from FDA RIHSC (Protocol #99-005-R, approval date: 5/11/99). The National Naval Medical Center Investigational Review Board, where the trial will be conducted, also approved the project. In this study, ultrasonic measurements (backscatter, attenuation, and sound speed) will be performed on 50 women ranging in age from 50–90. The objective will be to investigate the diagnostic utility of the backscatter measurement for diagnosis of osteoporosis.

In order to increase understanding of the fundamental mechanisms underlying the interaction between ultrasound and bone, preliminary experiments were conducted on bone samples in vitro. These experiments represent important steps in developing and optimizing data acquisition and analysis methodology for in vivo applications. They also increase understanding of how and why ultrasound bone sonometry is effective and should, therefore, lead to better reviews of these devices. This study has generated five papers, all submitted to scientific journals. In one paper, a theoretical model (with experimental corroboration) to explain the scattering properties of human trabecular bone was presented. In another paper, measurements of the temperature dependence of ultrasonic attenuation in human calcaneus were reported. A third paper presented a theory (with experimental substantiation) to explain the effects of frequency-dependent attenuation and dispersion on measurements of sound speed in calcaneus. A fourth paper

described an experimental comparison between various algorithms for measurement of sound speed in calcaneus. And a fifth paper reported an experimental correlation between bone mineral density and ultrasonic backscatter.

APPENDIX A - OST Publications

October 1, 1998 – September 30, 1999

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Landry RJ, Levin RE, Bergman RS. CIE photobiological lamp safety standard. Proceedings of the International Symposium and Workshop on Measurements of Optical Radiation Hazards, NIST, Gathersburg, MD (September 1-3, 1998), p289-294, published December 1, 1998.

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Merritt K, Woods TO, Brown SA, Hitchins VM. Re-use of devices: cleaning issues. Re-use of Single-use Devices meeting, Association for the Advancement of Medical Instrumentation, Crystal City, VA, May 5-6, 1999.

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Papaconstantinou AD, Brown KM, Fisher B, Umbreit T. The antiestrogen ICI 182.780 reverses the effects of B-estradiol on uterine morphology and stress protein levels. Society of Toxicology 38th Annual Meeting, 1999, *Toxicological Sciences* **48(1-S)**:135.

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Retta SM, Sagripanti JL. Mathematical model predicting the sporicidal activity of glutaraldehyde. FDA Science Forum, Washington, DC, (abstract) December 8-9, 1998.

Ruggera P, Carey C, Bassen H. A standard test method for evaluating *in vitro* implantable cardioverter defibrillator and cellular phone interaction. FDA Science Forum, Washington, DC, (abstract) December 1998.

Sagripanti JL, Johnson G, Almara A, Bockstahler LE. Radioactive versus luminescent detection of Junin virus after PCR amplification. FDA Science Forum on Biotechnology: Advances, Applications, and Regulatory Challenges, Washington, DC, abstract A13, p. 44, 1998.

Sagripanti JL. The FDA biochip for high throughput detection of infectious agents in FDA-regulated products as a perfect example of dual-use technology. Advanced Technology Application to Combat Casualty Care (ATACCC-98), Fort Walton, FL, 1998.

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Shope TB, Gagne RM. Regulatory initiatives and framework in the USA: special reasons for concern in interventional radiology. Does and Image Quality in Digital Imaging and Interventional Radiology, European Commission, Dublin, Ireland, June 24-26, 1999.

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Silberberg JL. IEC 60601-1-2: Improvements in the second edition and the FDA perspective. AAMI/FDA International Standards Conference, Crystal City, VA, (copies of overheads), March 17-18, 1999.

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Stewart SFC. Assessing the accuracy of color Doppler ultrasound. 1st Joint Meeting of BMES & EMBS, Biomedical Engineering Society (abstract), Atlanta, GA, 1999.

Tomazic VJ, Woolhiser MR, Beezhold DH. Quantification of latex proteins by inhibition ELISA. AAAAI Annual Meeting, Orlando, FL, February 1999.

Van Houten K, Sagripanti JL. High throughput screening of infectious agents: progress towards the FDA biochip. 32nd Middle Atlantic Regional Meeting, American Chemical Society Dickinson University, Madison, NJ, 1999.

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Wear KA, Wagner RF. Statistical properties of estimates of lesion detectability for medical ultrasonic imaging systems. Proceedings of the 24th International Symposium on Ultrasonic Imaging and Tissue Characterization, Arlington, VA, p. 66, June 2-4, 1999.

Witters DM. The future of wireless telemetry: concerns and solutions for electromagnetic interference (EMI). AAMI 99 Annual Meeting and Expo, Boston, MA, abstract p.10, June 1999.

Woods TO. The effect of specimen configuration and test velocity on suture tensile strength. 1998 FDA Science Forum on Regulatory Sciences, December 1998, p. 54, 1998.

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Woods To, Hitchins VK, Merritt K, Brown SA. Effect of use and simulated reuse on materials and PTCA balloons and catheters (percutaneous transluminal coronary angioplasty). Re-Use of Single-Use Devices Meeting, Association for the Advancement of Medical Instrumentation, Crystal City, VA, May 5-6, 1999.

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Schroeder L, Umbreit TH. Dioxin and tampons, 1999.

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Walsh DL, Schwerin MR. Effects of storage, materials, and stress on glove integrity: FY 99 progress report. DMMS Report #99-08.

APPENDIX B - OST Presentations

October 1, 1998 – September 30, 1999

Alqahtani J, McLean I, Weiblinger R, Ediger MN. Corneal ablation with low fluence excimer lasers. American Academy of Ophthalmology, Orlando, FL, October 24-27, 1999.

Bassen HI. Round table on worldwide standards harmonization – FDA engineering point of view. Round Table on Worldwide Standards Harmonization, Zagreb, Croatia, November 1998.

Bassen HI. The development of the IEEE-SCC34-2 SAR certification standard for wireless phones. Wireless Technology Research LLC, State of the Science Colloquium on the Health Impact of Wireless Technology, Washington, DC, 1999.

Bockstahler LE. Rapid detection of Mycobacterium tuberculosis mutants (presented to delegation of Russian molecular biologists). FDA/CDRH/Office of Science and Technology, Rockville, MD, February 9, 1999.

Bockstahler LE. Polymerase chain reaction, a rapid and sensitive molecular biology procedure applied to the detection of microorganisms. Alpha Chi Sigma (Chemistry) Fraternity, Washington Professional Chapter, American University, Washington, DC, February 17, 1999.

Brown SA. Metallic implant materials. International Agency for Research on Cancer (IARC), Lyon France, February 23-March 2, 1999.

Casamento JP. Measurements of magnetic fields emitted from electronic article surveillance systems (EASS) and summary of published in vitro studies of pacemaker interactions with EASS. '99 AAMI Annual Meeting and Expo, Boston, MA, June 1999.

Cerra F. Application of mammography beams at the FDA. AAPM annual meeting, Nashville, TN, July 27, 1999.

Chenault VM, Ansari RR, Ediger MN, King JF. Lasers from space to earth: looking at diabetes through the eye. Technology Transfer Society in the New Millennium, Technology Transfer Society, St. Pete Beach, FL, July 15-17, 1999.

Chenault VM. Unusual animal models: Psammomys obesus. National Capital Area Branch/American Association for Laboratory Animal Association for Laboratory Animal Science, Hagerstown, MD, September 30, 1999.

Chenault VM, DiCarlo C. Diabetic cataracts in Psammomys obesus (Sand Rat). US-Japan Cataracts Working Group, Kona, Hawaii, November 12-17, 1999.

Cyr WH, Miller SA. Estimates of UV doses and skin cancer from solar and sunlamp exposures. International Conference of Radiation Research, Dublin, Ireland, July 1999.

Ediger MN. Recent advances in biomedical applications of optics and lasers. Optical Society of America, Baltimore, MD October 6, 1998.

Ediger MM, Chenault VM. Dynamic light scattering from space to earth: looking at diabetes through the eye. Technology Transfer Society in the New Millennium, Technology Transfer Society, St. Petersburg, FL, 1999.

Gagne RM, Myers KJ, Wear KA, and Wagner RF. Model observers used for performance assessment of diagnostic imaging systems - and their statistical properties. 8th Far West Image Perception Conference, Calgary, Canada, May 1999.

Gagne RM and Shope TB. Regulatory initiatives and framework in the USA: interventional radiology. EC Workshop on Dose and Image Quality in Digital Imaging and Interventional Radiology, Dublin, Ireland, June 1999.

Godar DE. UVA1 radiation triggers two different final apoptotic pathways. Gordon Conferences, Colby-Sawyer College, New London, NH, June 27-July 16, 1999.

Goering PL. Metabolism and toxicology of mercury. Lecture to the Program in Toxicology, Graduate School, University of Maryland Medical Center, Baltimore, MD, November 4, 1998.

Harris GR. Effects of nonlinear propagation on measurement of the mechanical index. Twenty-second Annual Conference for Ultrasonics in Biophysics and Bioengineering, University of Illinois at Urbana, Monticello, Illinois, June 1-4, 1999.

Heaton HT. Medical subcommittee MPD accomplishments. Seventh Annual Meeting of Council of Ionizing Radiation Measurements and Standards (CIRMS), National Institute of Standards and Technology, Gaithersburg, MD, October 19-21, 1998.

Heaton HT. Some of FDA's concerns with low-energy brachytherapy sources. CIRMS Workshop: Low-energy Brachytherapy Sources, National Institute of Standards and Technology, Gaithersburg, MD, October 19-21, 1998.

Heaton HT. Dosimetry concerns for sources used in intravascular brachytherapy IDEs. Cardiovascular Radiation Therapy III (meeting), Washington, DC, February 17-19, 1999.

Heaton HT. Regulatory concerns with low energy brachytherapy sources. Council of Ionizing Radiation Measurements and Standards (CIRMS) Workshop on Low Energy Brachytherapy Seeds, Gaithersburg, MD, April 30, 1999.

Heaton HT. Regulatory issues with sources used in radiation brachytherapy. AAPM Annual Meeting, Nashville, TN, July 26-29, 1999.

Hellman KB. Tissue engineering and FDA perspective. FDA Science Forum, Breakout Session A: Therapeutic and Preventive Agents II – Tissue Engineering, Moderator's Introductory Remarks, Washington, DC, 1998.

Hellman KB. Advances in tissue engineering and regulatory considerations. BioConferences International, Inc., US Biotechnology Symposium, Washington, DC, November 29-December 1, 1998.

Hellman KB. TSE update: report on the University of Maryland/FDA (JIFSAN) workshop on TSE risks. Pharmaceutical Research and Manufacturers of America (PhRMA); Biological and Biotechnology Committee Fall Meeting, Washington, DC, October 1998.

Hellman KB. Charge and questions for the Committee. US Food and Drug Administration Public Meeting of the Transmissible Spongiform Encephalopathies Advisory Committee, Gaithersburg, MD, June 1999.

Hellman KB. FDA perspectives. Cambridge Healthtech Institutes Conference on TSEs, Washington DC, October 1999.

Hellman KB. FDA tissue engineering science and regulatory reform. FDA/PTEI Day, Rockville, MD, January 1999.

Hellman KB. Tissue engineered products and regulatory considerations. Course on Advances in Tissue Engineering, Rice University Institute of Biosciences and Bioengineering, Houston, TX, August 1999.

Hilbert SL, White J, Werkmeister J, Ramshaw J. Collagen distribution in heart valve leaflets. 4th Pan-Pacific Symposium, Connective Tissue Society, Queenstown, New Zealand, November 15-19, 1999.

Hutter JC, Luu HMD. Pharmacokinetic modeling of 4,4' – methylinidianiline (MDA) released from polyurethane medical devices. ASC Annual Meeting, Anaheim, CA, March 21-25, 1999.

Ilev I, Waynant RW. All fiber optic evanescent liquid level and leak. Conference on Lasers and Electro-Optics, Baltimore, MD, May 23-28, 1999.

Jennings RJ, Gagne RM. Objective approaches to the evaluation of mammographic phantom images. Division of Radiologic Physics, University of Virginia and Mid-Atlantic Chapter of AAPM, Charlottesville, VA, September 24-25, 1999.

Jones PL. Medical device software and the FDA. Army, ATACCC Conference, Ft. Walton Beach, FL, November 17-20, 1998.

Jones PL. US Army (WRAOR)/FDA cleanroom software engineering project. Army, ATACCC Conference, Ft. Walton Beach, FL, November 17-20, 1998.

Jones PL. A perspective on usage modeling and statistical testing. 21st International Conference on Software Engineering. ACM SIGSOFT, Los Angeles, CA, May 17-21, 1999.

Jones PL. Experience in programmable electronic safety. NIOSH-MSHA Workshop, Triadelphia, WV, August 17, 1999.

Jones PL. Software validation. Validation Forum '99, Arlington, VA, September 28, 1999.

Krauthamer V. Intracellular calcium dynamics in heart cells exposed to defibrillation shocks. 1999 Public Health Professional Conference, Alexandria, VA, June 1999.

Langone JJ. Guidance for immunotoxicity testing in FDA: Center for Devices and Radiological Health. Nineteenth Annual Meeting of the American College of Toxicology, Lake Buena Vista, FL, November 8-11, 1998.

Langone JJ. FDA/CDRH immunotoxicity testing guidance. American Society for Artificial Internal Organs (ASAIO) 45th Annual Conference, San Diego, CA, June 2-5, 1999.

Lao NT. Current status of ASTM method for measuring the amount of powder on medical gloves. The 1st Annual International Glove Conference and Trade Show, The Glove Shippers Association, Long Beach, CA, March 29-31, 1999.

Lao NT. Determination of ethylene oxide residuals in plasticized polyvinyl chloride and high-density polyethylene by headspace gas chromatography. AAMI Sterilization Standards Committee, EO Sterilization Residuals Working Group, Alexandria, VA, September 28, 1999.

Lucas AD, Wallis RR, Hutter JC, Kalson JA. Identifying toxic degradation products in cellulose acetate dialyzers. American Chemical Society 218th National Meeting, New Orleans, LA, August 22-26, 1999.

Luu HMD, Hutter JC. Pharmacokinetic modeling of 4,4' – methylinidianiline (MDA) released from polyurethane medical devices. ACS Annual Meeting, Anaheim CA, March 21-25, 1999.

Marlowe DE. Update on FDA modernization policy and standards recognition. 9th Annual AAMI/FDA International Standards Conference on Medical Devices, Arlington, VA, March 17, 1999.

Matsuzawa M, Tabata T, Kano M, Krauthamer V. Formation of functional synapses between identified CNN neurons *in vitro*. 29th Annual Neural Prosthesis Workshop, Bethesda, MD, October 1998.

Matsuzawa M, Tabata T, Kano M, Krauthamer V. Geometric control of neuronal growth and synapse formation. Biomedical Society, Cleveland, OH, November 1998.

Matsuzawa M, Potember R, Krauthamer V. Formation of physiologic synapses in culture. FDA Science Forum, Washington, DC, December 1998.

Merritt K. Animal models. Animal Models in Orthopaedics, Cambridge Health, Crystal City, VA, 1999.

Merritt K, Neale AR, Hitchins VM. Induction of TNF-a, IL-6 and nitric oxide by LPS in combination with AL_2O_3 and with polystyrene in RAW 264.7 murine macrophages. Gordon Conference on Biomaterials: Biocompatibility of Tissue Engineering, Holderness, NH, July 18-23, 1999.

Miller SA, Zmudzka BZ, Matchette SL, Beer JZ. Ultraviolet radiation exposure from diagnostic medical devices. International Workshop on UV Radiation Exposure, Oxford, United Kingdom, October 18-20, 1999.

Murray JF. Medical device software STOS. 1998 HIMA Medical Device Software Conference, Washington, DC, 1998.

Murray JF. Software engineering standards and medical devices. 9th Annual AAMI/FDA International Standards Conference, Arlington, VA, March 17, 1999.

Murray JF. IEC 60601-1-4: The FDA perspective. 9th Annual AAME/FDA International Standards Conference, Arlington, VA, March 18, 1999.

Phillips R, Heaton HT. FDA concerns with low-energy brachytherapy sources. CIRMS Meeting and Conference, National Institutes of Standards and Technology, Gaithersburg, MD, 1998.

Murray JF. Off-the-shelf software in medical devices: CDRH perspective and guidance. Biomedical Focus “99, American Society of Quality, St. Paul, MN, July 13, 1999.

Ravenscroft M, Krauthamer V, Hickman J. Silane-modified surfaces for templates for cell-based biosensors. FDA Science Forum, Washington, DC, December 1998.

Rudolph H. Risk management standards – impact on regulators. 9th Annual AAMI/FDA International Standards Conference on Medical Devices, Arlington, VA, March 17, 1999.

Rudolph H. Update on standards recognition under FDAMA. Medical Design and Manufacturing East, New York, NY, May 24-27, 1999.

Rudolph H. The use of standards in abbreviated 510(k)s. 1999 HIMA Device Submissions Workshop, Tysons Corner, VA, July 27-28, 1999.

Shope TB. FDA efforts to ensure Year 2000 compliance of medical devices and manufacturers. RX2000 Solutions Institute Special Interest Group Meetings, Dallas, TX, 1998.

Shope TB. Role of measurements and standards at FDA. Council on Ionizing Radiation Measurement Meeting, National Institute of Standards and Technology, Gaithersburg, MD, 1998.

Shope TB. The year 2000 date problem: medical device perspective (introductory remarks for panel session). PDA/FDA Joint Meeting Panel Discussion on Computer Systems Validation, Bethesda, MD, October 7, 1998.

Shope TB. FDA efforts to ensure Year 2000 compliance of medical devices and manufacturers.
RX2000 Solutions Institute Special Interest Group conference, Boston, MA, March 11-12, 1999.

Silberberg JL. The draft second edition of IEC 60601-1-2. Advances in wireless EMC. University of Oklahoma Center for the Study of Wireless EMC Forum #5, Arlington, VA, October 27-28, 1998.

Silberberg JL. IEC 60601-1-2: Improvements in the second edition and the FDA perspective. AAMI/FDA International Standards Conference, Crystal City, VA, March 17-18, 1999.

Silberberg JL. ANSI C63.18 recommended practice for ad hoc radiation. IEEE International Symposium, Seattle, WA, August 6, 1999.

Silberberg JL. The draft second edition of IEC 60601-1-2. IEEE International Symposium on EMC, Seattle, WA, August 2-6, 1999.

Sinciline D, Chenault VM. The care and use of a unique animal model of diabetes: Psammomys obesus. National Capital Area Branch/American Association for Laboratory Animal Science, Hagerstown, MD, September 28-30, 1999.

Stratmeyer ME, Brown RP. DEPH: Scientific and regulatory initiatives. Health Industry Manufacturers Association, Washington, DC, 1999.

Stratmeyer ME, Brown RP. Risk assessment-based approach for the evaluation of toxicity produced by compounds released from medical device materials. AAMI/FDA International Standards Conference, Crystal City, VA, 1999.

Walsh DL. Effects of oven aging on natural rubber latex fatigue and permeability. International Glove Conference, Long Beach, CA, 1999.

Waynant RW. Potentially new uses of laser-generated X-ray and X-ray lasers in medicine. Lasers and Electro-Optics Society, Orlando, FL, December 1-4, 1998.

Waynant RW, Gannot I, Ilev I. Mid IR waveguides and fibers for FEL laser surgery. International FEL Conference, Boston, MA, September 1999.

Waynant RW, Ilev I, Gannot I. Delivery systems for infrared laser therapy. New Concepts in Therapeutic Laser Applications, Optical Society of America, Munich, Germany, June 13-17, 1999.

Waynant RW. New methods of coupling infrared laser/fiber and fiber/handpiece for diagnostics and therapy. Advances in Optics of Biotechnology, Engineering Foundation, Kona, Hawaii, August 1-6, 1999.

Waynant RW, Ilev IK, Gannot I. Medical applications of infrared fibers and waveguides. Photonics East, SPIE, Boston, MA, September 20-23, 1999.

Wear KA and Wagner RF. Statistical properties of estimates of lesion detectability for medical ultrasonic imaging systems. Proceedings of the 24th International Symposium on Ultrasonic Imaging and Tissue Characterization, Arlington, VA, p. 66, June 2-4, 1999.

Weiblinger R, Ediger MN, Alqahtani J, McClean I. Corneal ablation with low fluence excimer laser. Annual Meeting, American Academy of Ophthalmology (AAO), Orlando, FL, October 24-27, 1999.

White J, Werkmeister J, Ramshaw J, Hilbert SL. Collagen distribution in heart valve leaflets. 4th Pan-Pacific Symposium, Connective Tissue Society, Queenstown, New Zealand, November 15-19, 1999.

Witter DM. Electromagnetic interference with medical devices: challenges for medical information technology. American Medical Informatics Association (AMIA) '98 Symposium, Orlando, FL, November 1998.

Witters DM. Wireless medical telemetry beyond the millennium: steps toward resolving electromagnetic interference (EMI) risks. Third Annual Conference, National Capital Health Care Engineering Society (NCHES), Arlington, VA, February 1999.

Witters DM. Electromagnetic interference with medical telemetry system: continuing challenges. Federal Communications Commission Forum on Medical Telemetry Washington, DC, November 1998.

Witter DM. Medical device electromagnetic compatibility: update of the FDA perspective. Advance in Wireless EMC Forum: Broad Applications, University of Oklahoma Wireless EMC Center, Arlington, VA, 1998.

Woods TO. ASTM task group on MR compatibility of implant material and medical devices. ISMRM Workshop on New Insight into Safety & Compatibility Issues Affecting In Vivo MR, Virginia, November 1-7, 1998.

APPENDIX C - Academic Affiliations of OST Staff

October 1, 1998 - September 30, 1999

Bassen, Howard	George Washington University Department of Electrical Engineering and Computer Science Adjunct Professor
Fischman, Gary S., Ph.D.	Johns Hopkins University Department of Engineering Instructor
	Catholic University of America Bioengineering Graduate Program Advisory Board
	Alfred University Biomaterials Program Advisory Board
Goering, Peter L., Ph.D.	University of Maryland School of Medicine Graduate Program in Toxicology Adjunct Professor
Grossman, Laurence W., Ph.D.	Georgetown University Medical Center Department of Radiology Adjunct Associate Professor
Hilbert, Stephen L., M.D., Ph.D.	Brown University School of Medicine Department of Surgery Division of Cardiothoracic Surgery Adjunct Professor (Research)
Krauthamer, Victor, Ph.D. for Health Services	Uniformed Services University Department of Physiology Adjunct Assistant Professor

Marlowe, Donald E.	Staff College Center for Devices and Radiological Health Food and Drug Administration Lecturer/Instructor
Myers, Kyle J., Ph.D.	Georgetown University Medical Center Department of Radiology Adjunct Associate Professor University of Arizona Optical Sciences Center Adjunct Professor
Picciolo, Grace L.	Clemson University Department of Bioengineering Adjunct Professor
Waynant, Ronald W., Ph.D.	Catholic University of America Electrical Engineering Department Adjunct Associate Professor Uniformed Services University of the Health Sciences Radiology Department

APPENDIX D - OST PATENTS

October 1, 1998 – September 30, 1999

None issued.

APPENDIX E - OST-Sponsored Research Seminars

October 1, 1998 – September 30, 1999

Bockstahler LE. Polymerase chain reaction, a rapid and sensitive molecular biology procedure applied to the detection of microorganisms. Alpha Chi Sigma (chemistry) Fraternity, Washington Professional Chapter, American University, Washington, DC, February 17, 1999.

Godar DE. National Institutes of Health. Shedding light on cell death: photons and apoptosis. Clinical Center, Bethesda, MD, September 15, 1999.

Hellman KB. Tissue engineering meetings. Gaithersburg, MD, September 13-14, 1999.

Korniewicz D, RN, DNSC, FAAN, University of Maryland, School of Nursing. Medical gloves. Center for Devices and Radiological Health, Rockville, MD, June 24, 1999.

Krauthamer V. Electrical stimulation, Science Grand Rounds. Center for Devices and Radiological Health, Rockville, MD, June 14, 1999.

Nelson JS, Beckman Laser Institute and Medical Clinic. Science seminar. Center for Devices and Radiological Health, Rockville, MD, May 27, 1999.

Picciolo G. Pittsburgh tissue engineering initiative. Center for Devices and Radiological Health, Rockville, MD, January 6, 1999.

Picciolo G. Tissue engineering seminar series. Center for Devices and Radiological Health, Rockville, MD, February-March 1999.

Werner T. GSF-National Research Center for Environment and Health, Munich, Germany. Can the specificity of computer-assisted promoter recognition reach a level useful for diagnostic application? Center for Devices and Radiological Health, Rockville, MD, October 28, 1998.

Witters D. Standards lecture. Center for Devices and Radiological Health, Rockville, MD, September 10, 1999.

APPENDIX F - Research Contracts and Interagency Agreements

October 1, 1998 – September 30, 1999

Air Force Office of Scientific Research (AFOSR) (FDA-224-98-6005). Infrared fiber and wavelength testing for the Air Force.

Armed Forces Institute of Pathology (AFIP) (FDA-224-82-5000). Tissue preparation and analysis of cardiovascular tissue specimens.

Biocon, Incorporated (FDA-223-99-6052). Housing, care, and welfare of experimental animals.

Department of Defense/Uniformed Services University of the Health Sciences (DOD/USUHS) (FDA-224-98-6015). Maintenance of an animal of the pathophysiology of diabetes for end organ studies.

Department of Energy/Oak Ridge Operations Office (DOE/ORISE) (FDA-224-88-6064). Establishment and conduct of a research fellowship program.

Environmental Protection Agency (EPA) (FDA-224-97-6010). Development of animal models for reproductive and developmental toxicity risk assessment.

National Aeronautics and Space Administration (NASA) (FDA-224-98-6013). Evaluation and testing of a novel fiber optic eye diagnostic instrument in an animal model of diabetes.

National Institute of Environmental Health Sciences (NIEHS) (FDA-224-94-6013). Effects of electro-magnetic fields on selected human cell lines.

National Institute of Health (NIH) (FDA-224-99-6008). Study factors that affect the performance of SMBG devices.

National Research Council (NRC) (FDA-223-99-6051). National Research Council Associateship Program for the Food and Drug Administration.

Naval Research Laboratory (NRL) (FDA-224-98-6019). Optical coherence tomography for medical applications.

Office of Naval Research (ONR) (FDA-224-92-6007). Waveguide and fiber optic delivery for medical applications of free electron lasers.

Safeskin Corporation (32-98). Increase in prevalence of latex protein allergy.

APPENDIX G - STANDARDS ORGANIZATIONS

October 1, 1998 – September 30, 1999

A. NATIONAL STANDARDS ORGANIZATIONS

Association for the Advancement of Medical Instrumentation (AAMI)
Apnea. Monitoring Committee
Biological Evaluation Committee
- Animal Protection Aspects WG (serves as US sub-TAG for ISO TC 194, WG 3)
- Cytotoxicity WG (serves as US sub-TAG for ISO TC 194, WG 5)
- Degradation Aspects Related to Biological Testing WG (serves as US sub-TAG for ISO TC 194, WG 2)
- Material Characterization WG
- Mutagenicity, Carcinogenicity, Reproductive Toxicity WG (serves as US sub-TAG for ISO TC 194, WG 6)
- Irritation & Sensitization WG (serves as US sub-TAG for ISO TC 194, WG 8)
- Sample Preparation & Reference Materials WG (serves as US sub-TAG for ISO TC 194, WG 12)
- Systemic Toxicity WG (serves as US sub-TAG for ISO TC 194, WG 7)
- Toxicokinetics Study Design WG
- WG 15 Strategic Approach to Biological Asessment

Cardiac Valve Prostheses Committee
ECG Committee
- Arrhythmia Monitoring WG (serves as US sub-TAG for IEC 62D, WG 2)
- Cardiac Monitor and Diagnostic ECG WG (serves as US sub-TAG for IEC 62D, WG 4/5)
- ECG Electrode WG (serves as US sub-TAG for IEC 62D, WG 6)
- Signal Averaging WG (serves as US sub-TAG for IEC 62D, WG 7)

EMC Committee
Electrical Safety Committee
International Standards Committee
Mechanical Circulatory Support Systems Committee
- SP10 Electronic or Automated Sphygmomanometers

Medical Device Software Committee
Neurosurgery Committee
- Implantable Neurostimulator WG (serves as US sub-TAG for IEC 62D, WG 2)

Pacemaker Committee (serves as US sub-TAG for ISO TC 150, SC 2, WG 2 & IEC 62D, WG 6)
Standards Board
Sterilization Standards Committee
- Microbiological Methods WG (serves as US sub-TAG for ISO TC 198, WG 8)
- Returned Devices Decontamination WG (serves as US sub-TAG for ISO TC 198, WG 80)
- Reusable Devices Resterilization WG (serves as US sub-TAG for ISO TC 198, WG 8 1)
- Reusable Supplies Decontamination WG (serves as US sub-TAG for ISO TC 198, WG 82)
- Sterilization Residuals WG (serves as US sub-TAG for ISO TC 198, WG 63)
  - Glutaraldehyde & Formaldehyde TG I (WG 63)

Waveform Testing Committee

American Institute of Ultrasound in Medicine (AIUM)
Board of Directors
Joint Standards Task Group - Safety Standard
Technical Standards Committee

Digital Measurement Subcommittee
Doppler Standards Subcommittee
National Electrical Manufacturers Association
Nomenclature Subcommittee
Scanner Equivalence Subcommittee

American National Standards Institute (ANSI)
Accreditation Committee
Acoustical Standards Management Board (ASA)
C 16 ESD Performance
C 63 Electromagnetic Compatibility
C 63.19 Task Group on Method of Measurements for Compatibility Between Wireless Communication Devices and Hearing Aids
SC 8 on Medical Device EMC Test Methods (WG on Ad Hoc EMC Measurement Techniques)
Executive Standards Council
Government Members Council
Healthcare Informatics Standards Planning Board
International Conformity Assessment Committee (ICAC)
Medical Devices Standards Board (MDSB)
N 43 Equipment for Non-Medical Radiation Applications
U.S. National Committee to IEC
Z 080 Ophthalmic Standards
Subcommittee for Medical Ophthalmic Products
Subcommittee for Ophthalmic Instruments
Subcommittee for Sunglasses and Fashion Eye Wear
Subcommittee on Eye Implants
Z80.7 IOL's
Operating Microscopes
Z 136 Biological Effects of Lasers
Z 136 Safe Use of Lasers Committee
Z 136.4 Laser Control Measurements Subcommittee
Z 3 11 Photobiological Safety of Lamps and Lighting Systems Subcommittee (IES)

American Society for Testing and Materials (ASTM)
Board of Directors
C 28 Advanced Ceramics
Committee on Technical Committee Operations (COTC)
D 11 Rubber
D 11.40 Consumer Rubber Products Condom Task Group
D 11.40 Consumer Rubber Products Latex Chemical Sensitivity Task Group
D 11.40 Consumer Rubber Products Latex Protein Task Group
D 11.40 Consumer Rubber Products Glove Task Group
E 28 Mechanical Testing
Committee on Technical Committee Operations (COTC)
E 28.03 Uniaxial Testing
E 36 Conformity Assessment
E 48 Biotechnology
E 48.02 Characterization and Identification of Biological Systems Subcommittee
E 48.02.03 Task Group on Viruses
F 04 Medical & Surgical Materials & Devices, Division I Resources
F 04.11 Polymeric Materials
F 04.11.04 Poly-L-Lactic Acid (PLLA)
F 04.11.05 Bioresorbable Polymer Terminology
F 04.11.06 Bioabsorbable Polymer-Degradation TM's
F 04.11.07 Acrylic Bone Cement
F 04.11.08 Revision of F648 UHMWPE

- F 04.12 Metallurgical Materials
- F 04.13 Ceramic Materials
  - F 04.13.04 Rev F603-Polycrystalline Alumina
  - F 04.13.05 Calcium Phosphate Coatings (CPC) Crystalline Characterization
  - F 04.13.09 Calcium Phosphate Coatings (CPC) Environmental Stability
  - F 04.13.10 Zirconia/Zirconium Oxide
- F 04.14 Composite Materials
  - F 04.14.01 Composite Hip Stem Testing
- F 04.15 Material Test Methods
  - F 04.15.03 Tension Testing Porous Materials
  - F 04.15.07 PLA Degradation
  - F 04.15.08 Coatings Abrasion
  - F 04.15.11 MR Compatibility of Implant Materials and Medical Devices
- F 04.16 Biocompatibility Test Methods
  - F 04.16.01 Biocompatibility Testing Relating to Particulate Implant Debris
  - F 04.16.05 Recovery of Foreign Particulates from Tissue
- F 04.18 Device Retrieval Analysis
- F 04.19 Corrosion of Implant Materials

F 04 Medical & Surgical Materials & Devices, Division II Orthopaedic Devices

- F 04.21 Osteosynthesis
  - F 04.21.01 Bone Screws
  - F 04.21.02 Bone Screw Testing Methods
  - F 04.21.03 Intramedullary Rods
  - F 04.21.04 External Fixation Devices
  - F 04.21.05 Bone Staples
  - F 04.21.06 Fixation Wires
  - F 04.2 1. 11 Bone Plates
- F 04.22 Arthroplasty
  - F 04.22.01 Total Hip w/ Femoral Stems
  - F 04.22.09 Femoral Stem Test Methods
  - F 04.22.10 Hip Wear
- F 04.25 Spinal Devices

F 04 Division III Medical/Surgical Devices

- F 04.30 Cardiovascular Standards (formerly F 04.40)
- F 04.31 Neurosurgical Standards (formerly F 04.50)
- F 04.33 Medical/Surgical Instruments (formerly F 04.65)
  - F 04.33.01 Needle Disposal/Puncture Resistance
- F 04.36 Cotton Products for Medical Use (formerly F 04.80)

F 04. Division IV Tissue Engineered Medical Products

- F 04.43.04 Alginate Task Group

F 04.10 Division IX Administrative

- F 04.90 Executive Subcommittee
- F 04.93.03 Neurosurgical Irnplants
- F 04.95 ISO/TC 168
- F 04.96 ISO/TC 194

F 12 Security Systems and Equipment

- F 12.60 Controlled Access Security, Search and Screening Equipment
- F 12.63 Task Group on Weapons Detection

F 23 Protective Clothing

- F 23.40 Biological

F 29 Anesthetic and Respiratory Equipment

- F 29.03 Division Three on Ventilators & Ancillary Devices
  - F 29.03.10 Pulse Oximeters

F 30 Emergency Medical Services

G 03 Durability of Non Metallic Materials

Institute of Electrical and Electronics Engineers (IEEE)
C 63 Electromagnetic Compatibility
C63.1 Electromagnetic Co mpatibility
C63.8 Medical Device Electromagnetic Compatibility Measurements
C 63.19 Task Group on Method of Measurements for Compatibility Between Wireless Communication
Devices and Hearing Aids
SC 8 on Medical Device EMC Test Methods
WG on Ad Hoc EMC Measurement Techniques
P 1140 Measurement of Electrical & Magnetic Near Fields in Frequency Range of 5Hz & 3 0MHz
P 1140.1 Measurement Techniques for ELF & VLF Magnetic Fields & Electric Fields from Desktop
Computer Displays & Associated Desktop Devices
SCC 28 Sectional Committee on Radiofrequency Radiation Hazards
SC I Subcommittee on Instrumentation
SC 2/3 Terminology Standards and Units of Measurement
SC 4 Safety Levels and/or Tolerances with Respect to Personnel
WG 03 High Frequency Effects (From Low Frequencies to and Including the Resonance Region)
SCC 28 Sectional Committee on Radiofrequency Radiation Hazards Executive Committee
SCC 34 Standards Coordinating Committee on Certification of Radiofrequency Safety Wireless Handsets
Software Safety Planning Group
Technical Committee on Ultrasonics, Ferroelectrics, and Frequency Control (UFFC)

Association for the Advancement of Rehabilitation Technology/Rehabilitation Society of North America (RESNA)

National Committee for Clinical Laboratory Standards (NCCLS)
Area Committee on Automation
Area Committee on Clinical Chemistry and Toxicology, Subcommittee on Determination of Lead
Subcommittee on Glycohemoglobin Measurements
Area Committee on Hematology, Subcommittee on Point-of-Care Hemostasis/Coagulation
Area Committee on Immunology and Ligand Assay Subcommittee on Digoxin
Area Committee on Microbiology Subcommittee on Culture Media
Area Committee on Molecular Methods
Subcommittee on Immunohistochemical Procedures
Subcommittee on Molecular Genetics
Subcommittee on Molecular Microbiology
Delegate
Standing Committee: International Relations (ISO TC 212)
Standing Committee: Nominating
Standing Committee: Standards Management

National Council on Radiation Protection and Measurements (NCRPM)
SC 66 Effects of Ultrasound

National Electrical Manufacturers Association (NEMA)
Digital Imaging and Communications Standards Committee WG 11 Display Function

Association for the Advancement of Rehabilitation Technology (RESNA)
Wheelchairs SC on Powered Wheelchair EMC

Underwriters Laboratory (UL)
Medical Industry Standards Group

United States Pharmacopeia (USP)

Official CDRH Correspondent

B. INTERNATIONAL STANDARDS ORGANIZATIONS

Deutsches Institut fur Normung (DIN) - German Institute for Standardization

AAE 9 Immunology, Serodiagnostics of Infectious and Immunological Diseases

ESD Association's Standards Committee

International Commission on Illumination (CIE)

Div. 6 - Photobiology and Photochemistry

ESD Association's Standards Committee

International Electrotechnical Commission (IEC)
TC 29 Electroacoustics WG 13 Hearing Aids
TC 56 Dependability WG 03 Equipment Reliability Verification
TC 61 Safety of Household and Similar Electrical Appliances
WG 16 Ultraviolet Radiation
SC 61B Safety of Microwave Ovens
TC 62 Electrical Equipment in Medical Practice
WG 02 Safety of Computer Systems Used in Medical Electrical Equipment
SC 62A Common Aspects of Electrical Equipment Used in Medical Practice TAG
Secretary's Advisory Group
WG 01 Safety
WG 13 Electromagnetic Co mpatibility
WG 15 Risk Management
WG 16 Electric Shock
WG 17 Mechanical Hazards
WG 18 Overheating, Fire Protection and Additional Hazards (combined WG 18 & 19)

SC 62B Diagnostic Imaging Equipment TAG \
WG 15 High Voltage Generators
WG 19 Mammographic Anti-Scatter Grids & Mammographic Cassettes
WG 22 Ultrasound Diagnostic Equipment
WG 24 Safety of X-ray Equipment for Interventional Procedures
WG 25 Safety of X-ray Equipment for Computed Tomography

SC 62C Equipment Radiotherapy, Nuclear Medicine and Radiation Dosimetry TAG
WG 03 Performance /of Dosemeters

SC 62D Electromedical Equipment TAG
WG 01 Multiparameter Patient Monitoring Equipment
WG 06 Cardiac Pacemakers
WG 11 Extra-corporal Shock Wave Lithotripsy Equipment sub-TAG
WG 01 Monitoring Equipment SC 62D Electromedical Equipment TAG
Electrocardiographs (ECG)
Multiparameter Patient Monitoring Equipment
Ultrasonic Medical Diagnostic Equipment
WG 02 Therapy and Surgery Equipment SC 62D Electromedical Equipment TAG
Ultrasound Therapy sub-TAG
TC 65 Industrial Process Measurement and Control, TC 65A Systems Aspects
WG 10 Functional Safety of Programmable Electronic Systems

TC 77 Electromagnetic Compatibility
TC 87 Ultrasonics
WG 08 Ultrasonic Field Measurement
WG 12 Ultrasound Exposure Parameters
U.S. Coordinating Committee on Electromagnetic Compatibility

ISBT Automation and Data Processing Working Group

International Organization for Standardization (ISO)
TC 056 Dependability WG 03 Equipment Reliability Verification
TC 150 Implants for Surgery
SC I Materials
SC 2 Cardiovascular Implants TAG
WG 01 Cardiac Valves
WG 02 Cardiac Pacemakers
WG 04 Blood Oxygenators
WG 05 Retrieval and Analysis of Implants
WG 09 Implant Data Sets
SC 3 Neurological Implants
SC 4 Bone and Joint Replacements
WG 02 Knee Wear
SC 5 Implants for Osteosynthesis
SC 6 Active Implants TAG WG 02 Cardiac Pacemakers (Joint ISO TC 150/SC 2-IEC SC 62D WG 6)
TC 157 Mechanical Contraceptives
WG 10 Latex Condoms, Minimum Burst Pressure and Burst Volume
WG 11 Latex condoms, Packaging Integrity
WG 12 Latex Condoms, Determination of the Amount of Lubricant
WG 13 Latex Condoms, Oven Treatment
WG 14 Latex Condoms, Guidance on the Use of ISO 4074
TC 172 Optics and Optical Instruments
SC 7 Ophthalmic, Optics and Instruments
WG 06 Ophthalmic Optical Instruments
WG 07 Eye Implants
SC 9 Electro-optical Systems (and Lasers)
WG 01 Terminology and Test Methods
WG 02 Interfaces and System Specifications for Lasers
WG 03 Safety
WG 04 Laser Systems for Medical Applications
WG 05 Laser Systems for General Applications
WG 06 Optical Components and Their Test Methods
WG 07 Electro-optical Systems Other Than Lasers
TC 173 Technical Systems and Aids for Disabled or Handicapped Persons
SC I Wheelchairs WG 10 Requirements and Test Methods for Electromagnetic Compatibility of Powered
Wheelchairs and Motorized Scooters
TC 194 Biological Evaluation of Medical Devices
WG 02 Degradation Aspects Related to Biological Testing Polymers Task Force
WG 02 Degradation Aspects Related to Biological Testing sub-TAG
TC 194 Biological Evaluation of Medical Devices
WG 02 Degradation Aspects Related to Biological Testing sub-TAG
WG 03 Animal Protection Aspects sub-TAG
WG 04 Clinical Investigations in Human Task Force on Systemic Toxicity
WG 05 Cytotoxicity sub-TAG
WG 06 Mutagenicity, Carcinogenicity, Reproductive Toxicity sub-TAG
WG 07 Systemic Toxicity sub-TAG

WG 08 Irritation, Sensitization
WG 11 Ethylene Oxide & Other Sterilization Process Residues (Joint TC 194-TC 198)
WG 12 Sample Preparation and Reference Materials
WG 13 Toxicokinetic Study
WG 14 Material Characterization
WG 15 Strategic Approach to Biological Assessment

TC 198 Sterilization of Health Care Products
WG 04 Biological Indicators sub-TAG
WG 08 Microbiological Methods sub-TAG
WG 12 Instructions for Processing of Resterilizable Medical Devices

TC 210 Quality Management and Corresponding General Aspects for Medical Devices
WG 02 General Aspects Stemming from the Application of Quality Principles to Medical Devices
WG 04 Application of Risk Management to Medical Devices

TC 212 Clinical Laboratory Testing with In Vitro Diagnostic Test Systems (NCCLS)

ISO/IEC
JTC1/SC7 TAG, Software Engineering

International Commission on Non-Ionizing Radiation Protection (ICNIRP) Standing Committee
3 – Physics and Measurements

APPENDIX H - Abbreviations and Acronmyms

AAMI	- American Association for Medical Instrumentation
AAPM	- American Association of Physicists in Medicine
ACCA	- Associate Commissioner for Consumer Affairs, OC, FDA, DHHS
ACF	- Administration for Children and Families, DHHS
ACCME	- Accreditation Council for Continuing Medical Education
ACHA	- Associate Commissioner for Health Affairs, OC, FDA, DHHS
ACLA	- Associate Commissioner for Legislative Affairs, OC, FDA, DHHS
ACMP	- American College of Medical Physicists
ACOM	- Associate Commissioner for Office of Management, OC, FDA
ACPA	- Associate Commissioner for Public Affairs, OC, FDA, DHHS (Press)
ACPE	- Associate Commissioner for Planning and Evaluation, OC, FDA, DHHS
ACPE	- American Council on Pharmaceutical Education
ACR	- American College of Radiology
ACRA	- Associate Commissioner for Regulatory Affairs, OC, FDA, DHHS
ADA	- American Dental Association
ADAMHA	- Alcohol, Drug Abuse, and Mental Health Administration, PHS, DHHS
AFGE	- American Federation of Government Employees (Union)
AFIP	- Armed Forces Institute of Pathology (located at WRAMC), DOD
AHA	- American Hospital Association
AHCPR	- Agency for Health Care Policy and Research, PHS, DHHS
AIMBE	- American Institute of Medical and Biological Engineering
AMA	- American Medical Association
ANSI	- American National Standards Institute
ARCRT	- American Registry of Clinical Radiography Technologists (MQSA)
ARPA	- Advanced Research Projects Agency
ARRT	- American Registry of Radiologic Technologists (MQSA)
ASH	- Assistant Secretary for Health, DHHS
ASPE	- Assistant Secretary for Planning and Evaluation, DHHS
ASPER	- Assistant Secretary for Personnel Administration, DHHS
ASTM	- American Society for Testing and Materials
BRMD	- Bureau of Radiation and Medical Devices, CANADA
CBER	- Center for Biologics Evaluation and Research, FDA, DHHS
CC	- Clinical Center (Warren Magnuson Clinical Center), NIH, DHHS
CEU	- Continuing Education Unit
CDC/CDCP	- Centers for Disease Control/Centers for Disease Control and Prevention
CENELEC	- European Committee for Electrotechnical Standardization (French term, English translation)
CDER	- Center for Drug Evaluation and Research, FDA, DHHS
CDRH	- Center for Devices and Radiological Health, FDA, DHHS
CFSAN	- Center for Food Safety and Applied Nutrition, FDA, DHHS
CIA	- U.S. Central Intelligence Agency (Headquarters: Arlington, VA)
CIRMS	- Council on Ionizing Radiation Measurements and Standards, NIST
CLIA	- Clinical Laboratory Improvement Amendments of 1988
CME	- Continuing Medical Education
CRADA	- Cooperative Research and Development Agreement
CRCPD	- Conference of Radiation Control Program Directors

CTIA - Cellular Telephone Industry Association
CVM - Center for Veterinary Medicine, FDA, DHHS
DASH - Deputy Assistant Secretary for Health, OASH, DHHS
DCP - Division of Commissioned Personnel, OASH, OSG (Parklawn Building)
DHHS - U.S. Department of Health and Human Services
DHSS - Department of Health and Social Security, ENGLAND
DOC - U.S. Department of Commerce
DOD - U.S. Department of Defense
DOL - U.S. Department of Labor
DOE - U.S. Department of Energy
DOT - U.S. Department of Transportation
ECRI - Emergency Care Research Institute (no longer uses name—initials only)
EEO - Equal Employment Opportunity Act
EMBS - Engineering in Medicine and Biology Society, IEEE
ERIM - Environmental Research Institute of Michigan
FAA - Federal Aeronautics Administration
FBI - Federal Bureau of Investigation, Department of Justice
FCC - Federal Communications Commission
FCCSET - Federal Coordinating Council for Science, Engineering and Technology,
FIC - Fogarty International Center, NIH, DHHS
FDLI - Food and Drug Law Institute
FDA - U.S. Food and Drug Administration, PHS, DHHS
FOIA - Freedom of Information Act
FTC - U.S. Federal Trade Commission
GAO - General Accounting Office
GC - General Counsel, FDA (now Office of Chief Counsel, FDA)
GPRA - Government Performance and Results Act
GPRE - Government Program Review and Evaluation
GSA - General Services Administration
HCFA - Health Care Financing Administration
HIMA - Health Industry Manufacturers Association
HRG - Health Research Group (Public Citizen: Ralph Nader-Dr. Sidney Wolfe)
(Consumers Health Political Action Committee - PAC)
HRSA - Health Resources and Services Administration, PHS, DHHS
ICRP - International Commission on Radiological Protection
ICRU - International Commission on Radiation Units and Measurements
IEC - International Electrotechnical Commission
IEEE - Institute of Electrical and Electronic Engineers, Inc.
IFIP - International Federation for Information Processing
IG - Inspector General, OIG, DHHS
IHS - Indian Health Service, DHHS
INNS - International Neural Networks Society
INS - U.S. Immigration and Naturalization Service
IOM - Institute of Medicine, NAS
IRB - Institutional Review Board
IRS - U.S. Internal Revenue Service
ISO - International Standards Organization

JCAHCA - Joint Commission on Accreditation of Health Care Organizations
NAAP - National Associatio n of Apnea Professionals
NAS - National Academy of Sciences
NBS - National Bureau of Standards, DOC (No longer exists: See NIST),
NCCLS - National Committee for Clinical Laboratory Science
NCHS - National Center for Health Statistics, CDCP, DHHS
NCHGR - National Center for Human Genome Research, NIH, DHHS
NCI - National Cancer Institute, NIH, DHHS
NCNR - National Center for Nursing Research, NIH, DHHS
NCRP - National Council on Radiation Protection
NCTR - National Center for Toxicological Research, FDA, DHHS
NEI - National Eye Institute, NIH, DHHS
NEMA - National Electrical Manufacturers Association
NHLBI - National Heart, Lung, and Blood Institute, NIH, DHHS
NIA - National Institute on Aging, NIH, DHHS
NIAAA - National Institute on Alcohol Abuse and Alcoholism, NIH, DHHS
NIAID - National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIAMSK - National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, DHHS
NICHHD - National Institute of Child Health and Human Development, NIH,
NIDCD - National Institute on Deafness and Other Communication Disorders, NIH, DHHS NIDA
NIDA - National Institute on Drug Abuse, NIH, DHHS
NIDDKD - National Institute of Diabetes and Digestive and Kidney Diseases, NIH NIDR
- National Institute of Dental Research, NIH, DHHS
NIEHS - National Institute of Environmental Health Sciences, NIH, DHHS
NIGMS - National Institute of General Medical Sciences, NIH, DHHS
NIMH - National Institute of Mental Health, NIH, DHHS
NINDS - National Institute of Neurological Disorders and Stroke, NIH, DHHS
NIH - National Institutes of Health
NIOSH - National Institute for Occupational Safety and Health, CDCP, DHHS
NIST - National Institute of Standards and Technology, DOC (formerly NBS)
NLM - National Library of Medicine, NIH, DHHS
NMQAAC - National Mammography Quality Assurance Advisory Committee, FDA
NRC - National Research Council
NRC - U.S. Nuclear Regulatory Commission
NSA - U.S. National Security Agency (Headquarters: Fort Meade, MD)
NSF - National Science Foundation
NOAA - National Oceanographic and Atmospheric Administration
NVLAP - National Association of Voluntary Laboratory Accreditation Practices
OC - Office of the Commissioner, FDA
OCA - U.S. Office of Consumer Affairs
OCC - Office of the Chief Counsel, FDA (formerly OGC)
OCR - Office for Civil Rights, DHHS
OHA - Office of Health Affairs, FDA, DHHS
OIG - Office of the Inspector General
OLA - Office of Legislative Affairs, OC, FDA, DHHS
OMB - Office of Management and Budget
OPA - Office of Public Affairs, OC, FDA, DHHS (Press Office/Relations)
OPE - Office of Planning and Evaluation, FDA, DHHS
ORA - Office of Regulatory Affairs, FDA, DHHS

OPM - Office of Personnel Management
OS - Office of the Secretary, DHHS
OSG - Office of the Surgeon General, PHS, DHHS (Commissioned Corps)
OSHA - Occupational Safety and Health Administration
PAC - Political Action Committee
PAHO - Pan-American Health Organization, WHO, UN
PHS - U.S. Public Health Service
RESNA - Rehabilitation Engineering Society of North America, ANSI
RSNA - Radiological Society of North America
SAMHSA - Substance Abuse and Mental Health Services Administration, DHHS
SCVIR - Society for Cardiovascular and Interventional Radiology
SMDA - Safe Medical Devices Act of 1990
SNL - Sandia National Laboratories
SPIE - Society of Photo-Optical Instrumentation Engineers
SSA - Social Security Administration (formerly part of DHHS)
SSRCR - Suggested State Regulations for Control of Radiation
UL - Underwriters Laboratories
UN - United Nations
USDA - U.S. Department of Agriculture
WCNN - World Congress of Neural Networks
WEAC - Winchester Engineering and Analytical Center, FDA, DHHS
WHO - World Health Organization, UN
WRAIR - Walter Reed Army Institute of Research, WRAMC, U.S. Army
WRAMC - Walter Reed Army Medical Center, U.S. Army

CDRH ABBREVIATIONS AND ACRONYMS

DDL - Devices and Diagnostics Letter (also known as The Orange Sheet) (Weekly Trade Magazine)
DCRND - Division of Cardiovascular, Respiratory and Neurological Devices, ODE
DCLD - Divison of Clinical Laboratory Devices, ODE
DECS - Division of Electronics and Computer Science, OST
DGRD - Division of General and Restorative Devices, ODE
DLS - Division of Life Sciences, OST
DMISS - Division of Management, Information and Support Services, OST
DMMS - Division of Mechanics and Materials Science, OST
DMQRP - Division of Mammography Quality and Radiation Programs, OHIP
DOD - Division of Ophthalmic Devices, ODE
DPS - Division of Physical Sciences, OST
DRAERD - Division of Reproductive, Abdominal, ENT, & Radiological Devices, ODE EIR - Establishment Inspection Report
EMC - Electromagnetic Capability
EMI - Electromagnetic Interference
ERC - NSF Engineering Research Center, Duke University (National Science Foundation)
510(k) - Five-Ten K: Premarket Notification of New Medical Device (Clearance Based on a Similar, Previously Cleared Device)
HL - High Level or High-Level Control
IDE - Investigational Device Exemption
IND - Investigational New Device (or Drug) (application for transitional

devices)

IAG - Interagency Agreement
kVp - Measurement of Meters (as in kVp Meters)
MDDI - Medical Devices, Diagnostics & Instrumentation (also known as The Gray Sheet) (Weekly Trade Magazine))
MDH - X-ray radiation instrument used by FDA in its inspections (originally marketed by a company called MDH)
MDR - Mandatory Device Reporting Program
MON - Memorandum (Memoranda) of Need
MQC - Mammography Quality Control (as in MQC Manual)
MQSA - Mammography Quality Standards Act of 1992
MRI - Magnetic Resonance Imaging (formerly nuclear magnetic resonance)
MRS - Magnetic Resonance Spectroscopy
NEXT - Nationwide Evaluation X-ray Trends (Data Bank)
NSWL - Naval Surface Warfare Laboratory (in White Oak, Silver Spring)
NVLAP - National Voluntary Laboratory Accredited Program, (NIST, DOC) (MQSA)
OCD - Office of the Center Director, CDRH, FDA, DHHS
OC - Office of Compliance, CDRH, FDA
ODE - Office of Device Evaluation, CDRH, FDA
OHIP - Office of Health and Industry Programs, CDRH, FDA
OSM - Office of Systems and Management, CDRH, FDA
OPA - Office of Public Affairs, FDA, DHHS (Press Office)
ORA - Office of Regulatory Affairs, FDA, DHHS (field offices)
OSB - Office of Surveillance and Biometrics, CDRH, FDA
OST - Office of Science and Technology, CDRH, FDA
PDP - Product Development Protocol
PMA/PMAA - Pre-Market Approval Application
PMS - Post-Market Surveillance
QA - Quality Assurance
QC - Quality Control
RIHSC - Research Involving Human Subjects Committee, FDA
ROC - Receiver Operating Characteristic Curve
RRHR - Regional Radiological Health Representative, FDA
SCLIR - Secondary Calibration Laboratories for Ionizing Radiation
SIDS - Sudden Infant Death Syndrome
TEPRSSC - Technical Electronic Product Radiation Safety Standards Committee, CDRH, FDA, DHHS
TMJ - Temporomandibular Joint
TQM - Total Quality Management